Infants with a birth weight ≤ 750g

Maternal characteristics, survival, neonatal morbidity and development

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Thesis, Utrecht University, with a summary in Dutch

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Kinderen met een geboortegewicht van 750 gram of minder
Kenmerken van de moeder, overleving, morbiditeit en ontwikkeling later
(met een samenvatting in het Nederlands)

Proefschrift

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Introduction

Introduction and outline of the thesis

Extremely low birth weight (ELBW) infants are defined, according to the World Health Organisation (WHO), as infants with a birth weight less than 1000 gram (g).[1]
The expected birth weight is depending on several factors such as gestational age, gender, parity, ethnicity, parental size, lifestyle, socio-economic condition and health. In a healthy pregnancy birth weight is gradually increasing with gestational age. A higher birth weight is expected in infants of male gender as well as in infants of multiparous women and in singleton pregnancies.
Obviously spontaneous preterm delivery or medically indicated preterm delivery as well as intra-uterine growth restriction (IUGR) may both result in ELBW infants.

Epidemiology of ELBW infants

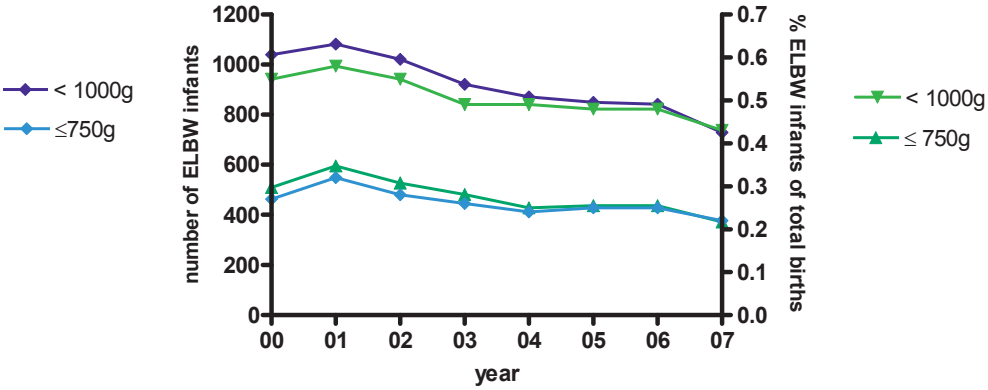
The Perinatal Registry of the Netherlands (PRN) showed that 6512 infants with a birth weight < 1000g were born between 2000 and 2007, this accounts for 0.45% of the total number of births (all birth weight categories, n= 1450365) in this time period. For infants with a birth weight ≤ 750g this percentage was 0.26%.[2] These data (including live and still born infants, born at a gestational age of ≥ 24 weeks) are presented in Figure 1.
According to the Annual summary of vital statistics of the United States of 2002 and 2003, less than 1% of the 4 million annual births in the United States were ELBW infants.[3,4] The Annual summary of vital statistics of the United States only reported a 12.7% rate of very low birth weight infants (< 1500g) in 2007.[5] Doyle et al. conducted a study on evaluation of neonatal intensive care for ELBW infants (birth weight 500-999g). They compared different eras: 1979-1980, 1985-1987, 1991-1992 and 1997. The annual rates of ELBW infants in these eras were 3.03, 3.06, 3.29 and 3.77 per 1000 live births respectively.[6] Avchen et al. presented a population based study of 267213 infants born between 1982 and 1984 in Florida, they showed that infants with a birth weight of ≤ 999g accounted for only 0.2% of the population.[7] All reports demonstrated that ELBW infants comprise only a minority of the general population. Nevertheless, attention for these infants continues to increase since obstetrical and neonatal care is changing towards more active treatment of infants born at extremely low gestational ages, resulting in an increased number of ELBW infants. Preterm delivery together with IUGR account for the majority of ELBW infants.

Preterm delivery

Epidemiology

Spontaneous preterm delivery (< 32 weeks) occurs in about 1% of singleton pregnancies, whereas multiple pregnancies account for 15 to 20% of all preterm births. Understandably, the incidence of early preterm delivery in multiple pregnancies is positively correlated to the number of fetuses.[8] In the Netherlands preterm delivery between 24 and 32 weeks gestational age occurred in 0.9% of singleton pregnancies and in 8.3% of the multiple pregnancies in 2007.[2]

Figure 1. ELBW infants live and still born at a gestational age ≥ 24 weeks in the Netherlands between 2000 and 2007.



The last decades the number of preterm born infants have increased. Doyle et al. reported the number of extremely preterm infants (22-27 weeks) born alive without lethal anomalies in 1997 and 2005 to be 217 and 270 respectively.[9] According to the Annual summary of vital statistics the rate of preterm delivery (< 32 weeks) in both singleton and multiple pregnancies the United States in 1990, 2006 and 2007 was 10.6%, 12.8% and 12.7% respectively.[4,5]

Recurrence risk of preterm delivery ranges from <10% to 60%, dependent on the number and gestational age of previous deliveries. Mercer et al. showed a 2.5 fold increase of preterm delivery in a subsequent delivery.[10,11]

Epidemiology

Preterm labour is thought to be initiated by multiple mechanisms, including infection, uteroplacental ischaemia or haemorrhage, uterine overdistension and stress. Furthermore, there are many maternal and fetal characteristics that have been associated with preterm birth, including maternal demographic characteristics (low socio-economic and educational status, low and high maternal ages and single marital status), nutritional status, pregnancy history, present pregnancy characteristics, cervical length, psychological characteristics and adverse behaviours (smoking, alcohol and drugs).[8, 12-15] The risk factors for premature delivery are summarized in Table 1.

Intra-uterine infection might account for 25 to 40% of the preterm births. The most commonly identified bacteria in preterm labour with intact membranes are Ureaplasma urealyticum, Mycoplasma hominis and Gardnerella vaginalis. Whereas group B streptococci and Escherichia coli are associated with preterm prelabour rupture of membranes and chorioamnionitis. Mechanism of preterm delivery due to infection include intra-uterine bacterial invasion, resulting in release of endotoxins,

exotoxins and cytokines. These toxins and cytokines stimulate synthesis and release of prostaglandins and metalloproteases. Prostaglandins stimulate uterine contractions and metalloproteases attack the chorioamniotic membranes and may lead to rupture of the membranes.[16]

Increasing maternal age is associated with an increased incidence of multiple pregnancies. Furthermore, increasing maternal age has contributed to an increasing use of assisted reproductive technologies, which are associated with multiple pregnancies; resulting in an increase of preterm deliveries. Vohr et al. showed that increased maternal age is also related to the occurrence of hypertensive disorders, which is a risk factor for IUGR, placental insufficiency and medically indicated preterm delivery.[17]

Ethnicity is also related to preterm delivery, as preterm birth rates are higher in black women (16 to 18%), compared to white women (5 to 9%).[8,18]

Vaginal bleeding caused by placental abruption or placenta previa, as well as vaginal bleeding in the first and second trimesters e.c.i. are associated with preterm delivery.[8,19]

Maternal medical conditions such as a history of cervical cone biopsy or anomalies of the uterus, diabetes, hypertension, thyroid disease and asthma are also associated with increased rates of preterm delivery.[8,20]

So, numerous characteristics are reported to be associated with preterm birth, but idiopathic preterm labour was shown to be the principle causative factor in 43% of all preterm deliveries.[13]

Furthermore, iatrogenic preterm delivery accounts for a substantial part of the preterm births as well. This is merely due to deteriorating hypertensive disorders, pre-eclampsia, eclampsia or HELLP-syndrome combined with IUGR.[8,17,24,25,30]

Intra-uterine growth restriction

Definitions for IUGR vary in the literature. However, the most commonly used definition is growth below the 10th centile.[21] Various pathogenic and etiologic factors for IUGR, divided in maternal, placental, uterine and fetal factors, have been identified (Table 1).

Pathogenesis

Fetal growth is regulated by different mechanisms including genomic, somatotrophic and developmental mechanisms of the placenta. Genomic mechanisms are of fetal, parental and placental origin. The presence of genomic imprinting results in differential expression of maternal and paternal genes. However, fetal growth is more dependent on the maternal phenotype. Furthermore, epimutations in the placenta may impede placental nutrient transport and lead to growth restriction. Somatotrophic mechanisms include the regulatory function of the insulin-like growth factor (IGF) system. Lower IGF-1 levels are observed in growth restriction, as well

as of placental growth hormone.[22]
Maldevelopment of the placenta is an important causative factor in fetal growth restriction. Due to absence of dilating remodelling of spiral endometrial arteries during pregnancy the uteroplacental flow impedance remains high and maternal blood flow into the intervillous spaces cannot increase. Furthermore, absence of fetal-placental angiogenesis due to dysfunction of vascular endothelial growth factor (VEGF), placental growth factor (P1GF) and their receptors results in abnormal villous growth and development. These two mechanisms results in deficient placental transport. A reduction of uterine perfusion decreases the fetal glucose and amino acid delivery and this leads to down regulation of both the insulin and IGF-1 endocrine axis and the hepatic glucose metabolism. This results in glycogenolysis and protein break down for gluconeogenic amino acids which eventually leads to growth restriction.[23]
Furthermore, structural abnormalities of the placenta (e.g. single umbilical artery, velamentous umbilical cord insertion, bilobate placenta, placental hemangiomas, infarcts or focal lesions) may also result in decreased placental perfusion and reduced fetal oxygenation.[24,25]

Etiology
It is important to distinguish between different causes for fetal growth restriction, as the treatment and prognosis is different in IUGR due to placental disease, compared with chromosomal disorders, viral infections or environmental factors such as smoking and substance abuse, socio-economic condition and altitude. Furthermore, one should keep in mind the possibility of constitutionally small for gestational age infants.[23-27]
The maternal causes for IUGR are usually related to reduced uteroplacental blood flow, reduced maternal blood volume, reduced oxygen-carrying capacity or decreased nutrition to the fetus. Hypertensive disorders, diabetes, renal insufficiency, systemic lupus erythematosus and antiphospholipid syndrome all result in a reduced uteroplacental blood flow. Living at high altitudes leads to a lesser pregnancy associated volume expansion and therefore a reduced blood volume and also a reduced oxygen-carrying capacity. The latter occurs also in cyanotic heart disease, lung disease, hemoglobinopathies and cigarette smoking. Decreased nutrition to the fetus is related to the maternal nutritional status, as poor weight gain during pregnancy or a low prepregnancy weight is associated with IUGR.[26,28,29]
Hypertensive disorders are present in 30 to 40% of pregnancies complicated with fetal growth restriction. Defective maternal placental vascular adaptation underlies chronic hypertension, gestational hypertension and pre-eclampsia.[29-31]
Cigarette smoking, alcohol consumption and cocaine use are also strongly associated with IUGR.[29,32,33]
And of course, multiple pregnancies account both for fetal growth restriction as for preterm delivery. Therefore, assisted reproductive technologies are also associated

with IUGR and premature delivery.
Furthermore, fetal growth restriction is related to congenital fetal anomalies, especially chromosomal abnormalities as well as perinatal infections (rubella, cytomegalovirus, human immunodeficiency virus, varicella-zoster, toxoplasmosis and malaria).[27,29,33-35]

Table 1. Risk factors for low birth weight infants due to preterm delivery or IUGR.[8-33]

	Preterm delivery	IUGR
Maternal		
Age (<16 or >40)	+	+
Altitude	-	+
Anaemia	-	+
Artificial reproductive technologies	+	+
Asthma	+	+
Autoimmune disorders (APS, SLE)	+	+
Cardiac disease	+	+
Cervix insufficiency	+	-
Diabetes (mellitus, gestational)	+	+
Ethnicity (negroid)	+	-
Hemoglobinopathy (sickle cell disease)	-	+
Hypertension (chronic, gestational)	+	+
Lifestyle (smoking, alcohol, drugs)	+	+
Malnutrition	+	+
Medications (anti-epileptic)	-	+
Multiple pregnancy	+	+
Peridontal disease	+	+
Pre-eclampsia	+	+
Previous IUGR infants	-	+
Renal disease	-	+
Short stature	-	+
Socio-economic status	+	+
Thrombophilia	-	+
Placental		
Abruptio placentae	+	+
Anomalies (accreta, circumvallata, previa)	+	+
Chorioamnionitis	+	+
Deciduitis	+	+
Hemangioma	+	+
Placentitis	+	+
Infarction	+	+
Placental cysts or tumours	+	+
Single umbilical artery	-	+
Thrombosis	+	+
Tumour	+	+

	Preterm delivery	IUGR
Uterine		
Arteriosclerosis of decidual spiral arteries	-	+
Myomas	+	+
Anomalies (septate uterus, synechia)	+	+
Fetal		
Chromosomal disorders (aneuploidy, trisomy 13, 18, 21, triploidy)	+	+
Congenital infections (TORCH)	+	+
Congenital malformations (gastroschizis, omphalocele, diaphragmatic hernia, congenital heart defect, Potter syndrome etc)	+	+
Hemolytic disease	+	+
Infections (malaria, parvo, HIV, hepatitis B, syfilis)	+	+
Metabolism disorders	-	+
Osteogenesis imperfecta	-	+

IUGR: intra-uterine growth restriction, APS: antiphospholipid syndrome, SLE: systemic lupus erythematosus, TORCH: Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, Herpes Simplex Virus, HIV*:* Human Immunodeficiency Virus.

Aims and outline of the thesis

Due to improvements in perinatal care survival of ELBW and extremely preterm infants has increased during the last decades. However, these infants remain at risk for serious neonatal morbidities and impaired mental and motor development as well as growth impairment.[36-48]

Since active obstetrical and neonatal care is changing towards treatment of infants born at extremely low gestational ages, the number of ELBW infants and the attention for these infants continues to increase.

We conducted a retrospective cohort study of ELBW infants with a birth weight ≤ 750g, born in a ten year study period between 1996 and 2005, in the Wilhelmina Children‘s Hospital in Utrecht, The Netherlands. The complete cohort is described as a whole and a comparison of two consecutive 5 year birth periods was made (cohort I: infants born between 1996 and 2000, and cohort II: infants born between 2001 and 2005) as well. Furthermore, a comparison of children who were appropriate for gestational age (AGA, birth weight ≥ p10) with children small for gestational age (SGA, birth weight < p10) was performed.

Chapter 2 contains a description of the follow-up assessments of cognitive and motor development and behaviour used in the study.

Chapter 3 describes the obstetrical history and obstetrical complications of the maternal population of our cohort of preterm infants with a birth weight ≤ 750 gram.

Chapter 4 reports on survival and neonatal morbidity.
Chapter 5 outlines neurodevelopmental outcome at 2 years corrected age in relation to neonatal morbidity.
Chapter 6 covers the neurodevelopmental outcome over time: at 2, 3.5 and 5.5 years of age.
Chapter 7 describes motor developmental outcome at 2, 3.5 and 5.5 years of age.
Chapter 8 gives insight in postnatal growth and its relation with cognitive and motor developmental outcome at 5.5 years of age.
Chapter 9 contains a summary, conclusions, general discussion and recommendations for further research.

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2

Follow-up assessments for cognitive and motor development of extremely low birth weight infants

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Introduction

Infants born at a gestational age below 30 weeks and/ or with a birth weight (BW) below 1000 gram who have been admitted to the Neonatal Intensive Care Unit (NICU) in our University Hospital were included in a standardized follow-up program. In our study cohort of extremely low BW infants (BW ≤ 750 gram, born between 1996 and 2005) the cognitive and motor development has been assessed at the corrected age (CA) of 2 years, and at the uncorrected age of 3.5 and 5.5 years. In this chapter the standardized follow-up assessments which were used are described.

At 2 years CA the cognitive and motor development was assessed using either the Griffiths Mental Developmental Scales (GMDS) from birth to 2 years or the Bayley Scales of Infant Development-second-Dutch edition (BSID-II-NL). The GMDS was used in the majority of the children between 1996 and 2000, and since December 2000 onwards the BSID-II-NL was used in our hospital. At 3.5 years of age the GMDS for 2 to 8 years was used. At 5.5 years of age cognitive development was assessed by means of an intelligence test, this was either the Revisie Amsterdamse Kinder Intelligentie Test (RAKIT) or the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) or the Snijders-Oomen Nonverbal Intelligence Test-Revised (SON-R). In our hospital the RAKIT was performed in the majority of the children. Since January 2008 the WPPSI-III (the Dutch experimental version based on English norms) was preferred as the RAKIT is less well-known internationally and the norms are rather dated. Furthermore, a more differentiated representation is achieved by using the WPPSI-III. In October 2009 the complete version of the Dutch WPPSI-III (including the Dutch norms) became available and is being used since November 2009 in our hospital. In six children the SON-R was used, five of these children were assessed in another institution were the SON-R was most commonly used.

Behaviour was also evaluated by means of the Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF), which were completed by the parents and teachers respectively, prior to the intelligence test. The Movement Assessment Battery for Children (M-ABC) was used to assess the motor development at 5.5 years of age. In 2007 a new version, the M-ABC-II became available and from October 2007 onwards this version was used in our hospital. An overview of the assessments used is presented in Figure 1.

Figure 1. Overview of the follow-up assessments used in our study population of ELBW children ≤ 750g born between 1996 and 2005.

2 years corrected age
-Cognitive and motor development
  -Griffiths Mental Developmental Scales- Revised (n=49)
  -Bayley Scales of Infant Development-II-NL (n=52)

3.5 years of age
-Cognitive and motor development
  -Griffiths Mental Developmental Scales- Extended revised (n=64)

5.5 years of age
-Cognitive development
  -Intelligence test
    -Revisie Amsterdamse Kinder Intelligentie Test (n=29)
    -Wechsler Preschool and Primary Scale of Intelligence (n=26)
    -Snijders-Oomen Nonverbal Intelligence Test- Revised (n=6)
-Behaviour
  -Child Behaviour Checklist (n=47)
  -Teacher Report Form (n=43)

-Motor development
  -Movement Assessment Battery for Children (n=50)
  -Movement Assessment Battery for Children-II (n=20)

Griffiths Mental Scales of Development

Griffiths Mental Developmental Scales: birth to 2 years[1,2,3]

The GMDS is used for the assessment of the cognitive development of babies and young children from 0 to 2 years of age. The GMDS can measure five areas of development as follows:

1. Locomotor: this subscale assesses gross motor skills, such as the ability to balance and to coordinate and control movements. The items include age-appropriate skills such as rolling, crawling, sitting, standing, and walking, even as more complex skills as walking up and down stairs, running and jumping.

2. Personal-social: this subscale measures the developing abilities that contribute to independence and social development. Items for the early months include visual recognition of the mother, following moving people with the eyes and using objects. Items at the older end of the 0-2 age range include asking for things, the ability to open a door and to assist in dressing or undressing oneself.

3. Hearing and language: this subscale assesses hearing (in the sense of active listening) and receptive and expressive language. At the younger end of the scale, items include searching for sounds, vocalisation other than crying and responding when being called. Age appropriate items for the latter months of the second year include listening to stories, identifying objects and use of word combinations.

4. Eye and hand coordination: this subscale focuses on fine motor skills, manual dexterity and visual monitoring skills. Early items include following a moving light with the eyes, looking at a toy momentarily when it is held up, and glancing from one object to another. In the second month the items start to include grasping and reaching for things. Age-appropriate items at the top of the 0-2 age range for this scale include building a tower of bricks and throwing a ball into a basket.
5. Performance: this subscale draws on the developing ability to reason through performance tests; the way in which manual skills are applied in novel situations and visual spatial skills, including speed and precision of working are assessed. Age appropriate items include clasping objects placed in the hand, dropping one cube for a second, unwrapping to find a hidden toy, putting a lid back on a box and opening a screw toy.

Procedure

A kit of standardized equipment is required to administer the items of the GMDS. Detailed instructions for using the equipment and scoring the items are given in the manual. The assessment at 2 years of age takes approximately 50-60 minutes.

Scoring

Raw scores for each individual subscale are computed by adding the total number of items passed. The raw scores from all the subscales are added to obtain a total raw score. The raw scores can be converted into age equivalent scores, which are presented in a table in the manual. Sub-quotients for each subscale can be calculated by dividing the age equivalent score by the chronological age and multiplying by 100. In case of assessing a preterm child, the CA may be used as well in the first two years of life. The general quotient is calculated by adding all subscale age equivalents, dividing by the number of subscales, and then dividing the total age equivalent by the chronological age or CA, and multiplying by 100. The sub-quotients and general quotient have a mean of 100 and a standard deviation (SD) of 12. A score of 100 indicates average performance of a child at a given age. Scores can be interpreted according to Table 1.

Table 1. Interpretation of the GMDS (birth to 2 years) quotients.

Quotient	Interpretation
≥ 112	accelerated performance
88-111	within normal limits
76-88	mildly delayed performance
< 76	significantly delayed performance

Norm, reliability and validity

The GMDS was published in 1996, and the normative information was based on a standardization sample which consisted of 665 children (366 boys and 299 girls) from the UK aged 0 to 2 years. The number of children tested in each two-month age band ranged from 47 to 62.[1,2]

In the Netherlands developmental tests are commonly judged by the Cotan system. This system consist of a standardized method to judge the quality of a developmental test by examining the norms, reliability and validity among others.[10] The GMDS has not been judged by Cotan, however Luiz et al.[4] showed good construct validity and good predictive validity was reported by Barnett et al.[5] Nevertheless, these authors suggest that the norms should be revised, as an upward drift in the mean scores has been identified.

Griffiths Mental Developmental Scales: 2 to 8 years[3]

This version of the GMDS is used for measuring the degree of development of young children from 2 to 8 years. The GMDS is composed of 6 subscales: the similar five subscales as used in the GMDS from birth to 2 years and one additional subscale: *Practical reasoning*. This sixth subscale assesses the ability to solve practical problems, understanding of basic mathematical concepts and understanding of moral issues. However, in our study we did not include this subscale in the developmental quotient at 3.5 years of age in order to make a good comparison with the neurodevelopmental outcome at 2 years CA, and because quite a number of practical reasoning scores were missing.

Procedure and scoring

The procedure and scoring are similar to the GMDS from birth to 2 years. The sub-quotients and general quotient have a mean of 100 and a SD of 15. Scores can be interpreted according to Table 2.

Table 2. Interpretation of the GMDS (2 to 8 years) quotients.

Quotient	Interpretation
≥ 115	accelerated performance
85-114	within normal limits
70-84	mildly delayed performance
< 70	significantly delayed performance

Norms, reliability and validity

Normative information for the GMDS from 2 to 8 years is based on a national standardization sample of 1026 children aged 2 to 8 years from the UK. Reliability has been found to be acceptable and the validity satisfactory.[2,3]

Bayley Scales of Infant Development-Second edition-NL[6,7,8,9]

The Dutch version of the Bayley Scales of Infant Development-Second Edition (BSID-II-NL) offers a standardized assessment of cognitive and motor development for children aged 1 month through 42 months. The BSID-II-NL includes a Mental Scale and a Motor Scale.

-*Mental Scale:* the mental scale yields a normalized standard score called the Mental Development Index (MDI), evaluating a variety of abilities: sensory/ perceptual acuities, acquisition of object constancy, memory, learning, problem solving, vocalization, beginning of verbal communication, basis of abstract thinking, habituation, mental mapping, complex language and mathematical concept formation.

-*Motor Scale:* the motor scale also yields a normalized standard score called the Psychomotor Development Index (PDI) and assesses the following skills: degree of body control, large muscle coordination, finer manipulatory skills of the hands and fingers, dynamic movement, dynamic praxis, postural imitation and stereo gnosis.

Procedure

The mental scale consists of 146 items and the motor scale of 96 items. The items are age-specific, therefore not all items will be assessed in a test session. A table in the manual indicates the numbers of the start and stop items based on the child's age at testing. The assessment at 2 years CA takes approximately 60 minutes.

Scoring

The child's raw scores on the Mental and Motor Scales of the BSID-II-NL are computed by adding the total number of items for which the child receives credit on each scale and all items below the basal item (the first item in the item set for which the child receives credit for a sufficient number of items). In the manual, tables are provided to convert raw scores for the Mental and Motor Scales to MDI and PDI scores. The child's age in years, months and days determines which page of the table should be used. The MDI and PDI scores both have a mean of 100 and a SD of 15. A score of 100 on either of the two scales indicates average performance of a child at a given age on that scale. By definition, in a normal distribution about two thirds of all children obtain scores between 85 and 115 (-1 SD and +1 SD respectively) and about 95% score in the 70-130 (-2 SD and +2 SD respectively) range. Scores can be interpreted according to Table 3.

Table 3. Interpretation of the BSID-II-NL MDI and PDI.

MDI / PDI	Interpretation
≥ 115	accelerated performance
85-114	within normal limits
70-84	mildly delayed performance
< 70	significantly delayed performance

Norms, reliability and validity

The BSID-II-NL was published in 2000, and was normed on a sample of 2000 Dutch children aged 1 month to 42 months. The BSID-II-NL has been judged by Cotan as sufficiently reliable but the predictive validity ranged from sufficient to insufficient.[9,11]

Intelligence tests

Revisie Amsterdamse Kinder Intelligentie Test[12]

The Revisie Amsterdamse Kinder Intelligentie Test (RAKIT) is used for measuring the intelligence of children aged four to eleven years, and originally consists of 12 subtests. The abbreviated version, which was used in our study, is suitable for children age 5:2 to 11:2 years. This version consists of the following 6 subtests:

1. *Exclusion:* out of four abstract figures, the child selects the one that is different from the other three.
2. *Verbal meaning:* words are presented to the child in an auditory fashion and from four figures the child chooses the one which resembles the word just heard.
3. *Disks:* putting disks with two, three or four holes on a board with pins as fast as possible until three layers of disks are placed on the board.
4. *Learning names:* memorizing the names of different animals using pictures presented on cardboard.
5. *Hidden figures:* discovering which out of six figures is hidden in a complex drawing.
6. *Idea production:* naming of as many words, objects or situations as possible that can be associated with a broad category within a certain time span, for example: “What can you eat?”

Procedure and scoring

A score form and a pen is required, the assessment at 5.5 years of age takes 45 to 150 minutes. Raw scores are computed by adding the subtest scores. Raw scores are converted to standard scores by using look-up tables in the manual. The sum of the standard scores is converted to an intelligence quotient (IQ).

Norms, reliability and validity

The RAKIT was published in 1984 and was normed on a random sample of 1415 Dutch children aged 4 to 11 years attending a regular primary school.[12] Reliability and validity of the RAKIT have been judged as good by Cotan.[11]

Wechsler Preschool and Primary Scale of Intelligence – Third Edition[13]

The Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III) is used for measuring the intelligence of children aged 2:6 to 7:11 years. An edition for young children aged 2:6 to 3:11 years and an edition for older children aged 4 to 7:11 years are available. The WPPSI-III originally consists of 14 subtests. The experimental Dutch version of the WPPSI-III (based on English norms) was

mainly used in our study population. This experimental version is composed of the 7 core subtests, on which the IQ is computed and one additional test: *Symbol search.*
1. Block design: while viewing a constructed model or a picture, the child uses one- or two-colour blocks to re-create the design within a specified time limit.
2. Information: for picture items, the child responds to a question by choosing a picture from four response options. For verbal items, the child answers to questions that address a broad range of general knowledge topics.
3. Matrix reasoning: an incomplete matrix is presented, the missing portion from 4 or 5 response options must be selected.
4. Vocabulary: for picture items, the child names pictures that are displayed. For verbal items, the child gives definitions for words that the examiner reads aloud.
5. Picture concepts: two or three rows of pictures are presented, the child has to chose one picture from each row to form a group with a common characteristic.
6. *Word reasoning:* the child is asked to identify the common concept being described in a series of increasingly specific clues.
7. Coding: copying symbols that are paired with simple geometric shapes.
8. Symbol search: the child has to indicate whether a target symbol matches any of the symbols in a search group.

Procedure and scoring
A score form and a pen is required, as well as the stimulus book. The assessment takes about 60 minutes. The WPPSI-III provides three IQ scores: a Verbal IQ, a Performance IQ score and a Full Scale IQ, as well as the processing speed.

Norms, reliability and validity
The WPPSI-III-NL was published in October 2009 and was normed on a random sample of 825 Dutch children aged 4 years to 7:11 years.[13] Reliability and validity of the WPPSI-III have been judged as sufficient to good by Cotan.[11]

Snijders-Oomen Nonverbal Intelligence Test- Revised[14,15]
The Snijders-Oomen Nonverbal Intelligence Test- Revised (SON-R) is used to measure general intelligence in children. Two versions are available for children aged 2:6 to 7 years and for 5:6 to 17 years. With children of about 5 years of age it would in general be better to use the SON-R 2.5-7. At 6 years of age both tests are well suited, whereas for 7 year old children, the use of the SON-R 5.5-17 is recommended, unless one suspects that the child lacks sufficient cognitive abilities. The first version consists of the following 6 subtests:
1. Mosaics: copying different mosaic patterns in a frame using red, yellow and red/yellow squares.
2. Categories: sorting cards into two groups according to the category to which they belong. Three pictures of objects have something in common. From a series of five

pictures, two must be chosen that have the same thing in common.
3. Puzzles: puzzle pieces (three to six) must be laid in a frame to resemble a given example.
4. Analogies: sorting discs into two compartments on the basis of form and/or colour and/or size.
5. *Situations:* half of each of four pictures is printed, the missing halves must be selected from a number of alternatives and must be placed within the correct pictures.
6. Patterns: copying simple and more complex patterns.
The second version consists of 7 subtests, the 6 described above and *Story telling* as an additional subtest: in which the child has to tell as much as possible about a picture on a board and what could happen to the persons or objects in the picture.

Procedure and scoring
The first version takes about 50 minutes and the second about 90 minutes. A SON-IQ can be computed from the scores on the subtests.

Norms, reliability and validity
The revised version of the SON 2.5-7 (SON-R) was published in 1998 and normed on a national random sample of 1124 Dutch children aged 2:3 to 7:3 years.[14,15] Reliability and validity of the SON-R have been judged as good by Cotan.[11]

Interpretation of IQ scores
All three intelligence tests described above have a mean IQ (±SD) for the general population of 100 (±15). For the interpretation of the IQ scores Table 4. was used:[16]

Table 4. Interpretation of IQ scores.

IQ score	Interpretation
> 130	very talented
121-130	talented
111-120	above average
90-110	average
80-89	below average
70-79	low talented
50-69	mild intellectual disability

Child Behaviour Checklist and Teacher Report Form [17]
The Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF) are widely-used for identifying problem behaviour in children. The first should be completed by the parents and the second by the teacher. The preschool checklist (CBCL/1.5-5) is

intended for use with children aged 18 months to 5 years, and the school checklist is meant for children aged 6 to 18 years (CBCL/6-18). Both checklists comprise of 100 questions and statements about the child's behaviour. Responses are recorded on a scale comprised of: 0 = Not True, 1 = Somewhat or Sometimes True, 2 = Very True or Often. Similar questions are grouped into a number of syndromes, e.g. aggressive behaviour, and their scores are summed to produce a score for that syndrome. Some syndromes are further summed to provide scores for Internalizing and Externalizing problem scales. A total score from all questions is also derived. For each syndrome, problem scale and the total score, tables are given that determine whether the score represents normal, borderline, or clinical behaviour. For the subscales a normal score is defined as below 65, borderline clinical range as between 65 and 70 and clinical range as over 70. For the internalizing and externalizing scales and the total score a normal score is defined as below 60, borderline clinical range as between 60 and 63 and clinical range as over 63.
Completion of the checklist takes approximately 15 minutes.

Reliability and validity
The reliability of the CBCL was judged as good by Cotan and the validity as sufficient.[11]

Movement Assessment Battery for Children
Movement-ABC[18,19]
The M-ABC indicates motor functioning in daily life. Four age bands are available: 4-6 years, 7-8 years, 9-10 years and 11 and older. Each age band contains eight age appropriate physical test items, divided into three sections: manual dexterity, ball skills, and static and dynamic balance. There are two sorts of tasks at each item level: time related (scored in seconds) and error related (scored by the number of ''good'' attempts or number of failures). At 5 years of age three items are used to assess manual dexterity: putting coins in a slit with both hands separately as fast as possible, threading beads as fast as possible and drawing between two lines as accurately as possible (number of failures). Two ball skills are tested by means of catching a bean bag (number of successes out of 10 trials) and rolling a ball through a goal (number of successes out of 10 trials). Finally, three static and dynamic balance items are evaluated by standing on one foot (number of seconds), hopping over a cord (number of good attempts of three) and heel-to-toe walking forwards over a line (number of good steps). The assessment takes approximately 30 minutes.

Scoring
The raw score of the best attempt on each item is converted into a scaled score.
For each item, scaled interval scores are provided: 0=good and 5=very poor. A separate score for all three sub-sections (manual dexterity, ball skills, and static and

dynamic balance) and a total impairment score (summation of the three sub-section scores) can be computed. The sub-section scores and the total impairment score (TIS) can be compared to normative tables to determine the percentile norm and standard deviation scores.

Interpretation

High scores represent poor performance. The sub-section scores and the TIS should be classified according to Table 5.

Table 5. Interpretation of the M-ABC scores.

M-ABC percentile score	Interpretation
> p15	normal
p6 – p15	at risk
≤ p5	abnormal

Reliability and validity

The M-ABC was published in 1992. The Dutch manual and norms became available in 1998. The normative sample consisted of 1234 children aged 5 to 9 years from the US.[18] The American norms are considered to be valid for the Dutch population. The overall validity and reliability of the M-ABC is considered to be good with a test-retest agreement of 97% at 5 years of age.[11,18]

Movement ABC-II[20]

The M-ABC-II is available for three age bands: 3-6 years, 7-10 years and 11-16 years. As in the original M-ABC described above, every age band consists of 8 standardized motor tasks, which assess Manual Dexterity, Ball Skills, Static and Dynamic Balance. The main changes between the M-ABC and the M-ABC-II are that the assessment has been reduced from 4 to 3 age bands. In addition, the age range has been extended upwards and downwards to run from ages 3-16 years. At 5 years of age, 3 items have been changed: the shape of the drawing trail (manual dexterity), rolling a ball into a goal has been replaced by catching a beanbag and throwing a beanbag in a circle (aiming & catching) and jumping over the cord has been altered in jumping on mats (balance). The assessment takes approximately 30 minutes.

Scoring

The best and fastest scores of two attempts are used as raw scores. The raw scores for each item are converted to standard score equivalents. Per sub-section the standard scores are added, and for computing a total test score, the scores of the three sub-sections should be summed. The sub-section and total standard scores and their equivalent percentiles are provided in the manual. Standard scores for the

individual items, for the three components and for the Total Test Score are based on a distribution with a mean of 10 and a standard deviation of 3.

Interpretation

The higher the total score, the poorer the performance. As for the M-ABC, the M-ABC-II classifies motor performance in the following categories: normal (> p15), at risk (p6 – p15) and abnormal (≤ p5).

Reliability and validity

The M-ABC-II was published in 2007 and was normed on 1172 children aged 3 to 16:11 years from the US. There is limited research on the content, concurrent, and construct validity of the M-ABC-II in study populations with sufficient numbers of participants. However, the authors consider the item content of the M-ABC and the M-ABC-II to be sufficiently similar and therefore reliability and validity of the M-ABC may be generalizable to the M-ABC-II.[18,20,21]

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3

Maternal characteristics of a cohort of preterm infants with a birth weight ≤ 750 gram

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Abstract

Objectives To describe the obstetric complications of women who delivered an extremely low birth weight infant. To compare two consecutive five year periods and appropriate versus small for gestational age infants (AGA: birth weight (BW) ≥p10, SGA BW <p10).

Study design Descriptive study of women (n=261) who delivered an infant ≤750g between 1996-2000 (cohort I, n=145) and 2001-2005 (cohort II, n=116) in the University Hospital Utrecht, the Netherlands.

Results 84.3% of the multigravids (n=121) had a complicated obstetric history: 46.3% miscarriage(s), 22.3% preterm delivery and 16.5% hypertensive disorders. In the index pregnancies (n=261) most prevalent complications were hypertensive disorders (52.1%, more in cohort II (p=0.002) and SGA (p=0.007)), fetal distress (39.5%) and intra-uterine growth restriction (32.6%). Resulting in a caesarean section in 47.9% and a spontaneous vaginal delivery in 19.2%. Intra-uterine deaths occurred in 35.2%, merely due to placental insufficiency (59.8%) and termination of pregnancy because of deteriorating hypertensive disorders (23.9%).

Conclusions A high percentage of parous mothers had serious complications in their obstetric history. The index pregnancy was largely complicated by hypertensive disorders. The majority of the infants with a birth weight ≤750g are growth restricted due to placental insufficiency. Follow-up of these infants is extremely important to evaluate neonatal morbidity and neurodevelopmental outcome.

Introduction

The number of extremely low birth weight (ELBW) infants and extremely preterm infants admitted to Neonatal Intensive Care Unit (NICU) has increased over the last decades. In the paediatric literature the main focus in these infants has been on survival and short and long term morbidity.[1-5] In the obstetric literature there are numerous studies on obstetric complications and their relation with low birth weight and preterm delivery. It is well known that gestational hypertension and pre-eclampsia, especially when occurring in early pregnancy, are strongly associated with placental insufficiency, fetal growth restriction and low birth weight. Data on recurrence rate of gestational hypertension and pre-eclampsia in a subsequent pregnancy are also well established.[6-10] Early spontaneous preterm delivery (< 32 weeks) occurs in about 1% of singleton pregnancies.[11] Preterm labour is associated with multiple gestation, hypertensive disorders, antepartum haemorrhage, preterm premature rupture of membranes and intra-uterine infection, but according to Slattery et al. idiopathic preterm labour was shown to be the principle causative factor in 43% of all preterm deliveries.[12]

The incidence of early preterm delivery in multiple pregnancies is higher and depending on the number of fetuses. In the Netherlands approximately 15% of the women with a multiple pregnancy deliver before 34 weeks of gestation.[13] The rates of preterm delivery in the Unites States were 57.4% for twins and 92% for triplets as compared with 10.4% for singletons.[14] So there are several obstetric complications that can result in either low birth weight or (extremely) preterm birth.[11-14]

However, to the best of our knowledge there are no data on the obstetric history and obstetric complications of a cohort of women delivering ELBW infants.

So when we started our descriptive retrospective study on infants with a birth weight ≤ 750 gram (g) the objectives were plural. This part of the study describes the maternal population with the emphasis on obstetric history and obstetric complications in the index pregnancy. Possible differences between the data of the two consecutive five-year periods are assessed, as well as the differences between the appropriate (AGA) and small for gestational age (SGA) infants.

Material and methods

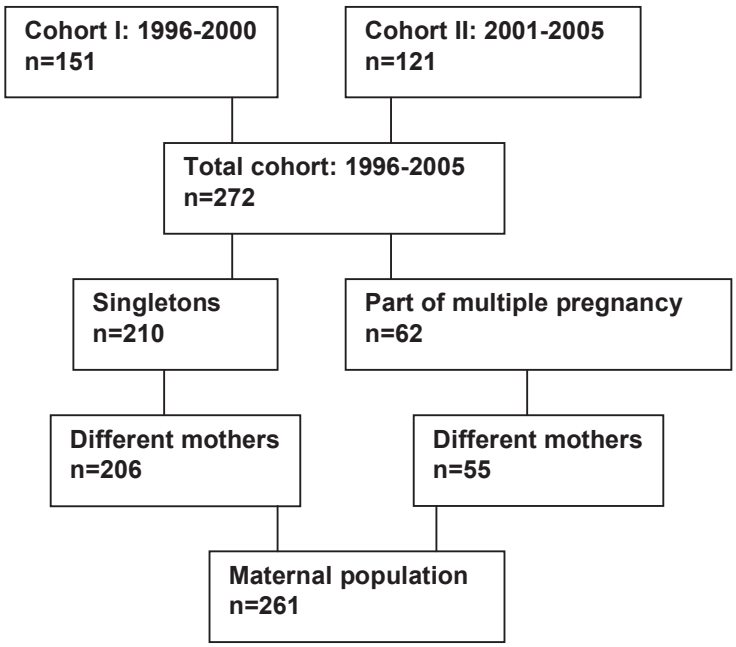
Subjects

All neonates with a birth weight of 750g or less and a gestational age (GA) of at least 24 completed weeks, born in 1996 through to 2000 (cohort I, n=151) and 2001 through to 2005 (cohort II, n=121) in the Wilhelmina Children's Hospital (tertiary referral centre) in the Netherlands, were eligible for this study. Neonates born at 24 completed weeks or more, but who died in-utero before 24 completed weeks were excluded. Infants born with congenital or chromosomal disorders were excluded.

272 infants were in accordance with our inclusion and exclusion criteria. However,

these infants consisted of 210 singletons born out of 206 different mothers (in our ten year study period one mother delivered 4 singletons, and one delivered 2 singletons). 62 infants were part of a multiple pregnancy: 56 belonged to a twin pregnancy, born out of 50 different mothers (of 6 twin pregnancies both children were included) and 6 belonged to a triplet pregnancy, born out of 5 different mothers (two children of the same triplet were included).
In order not to calculate any important event twice, only the firstborn was included in the analysis. After this calculation our final maternal population consisted of 261 (206 + 50 + 5). different mothers (Figure 1).

Figure 1. Study population of infants with a birth weight ≤ 750g born in 1996-2005.



Data collection and definitions
Maternal and neonatal data were collected by reviewing the medical charts and were entered in the dataset. The maternal data comprised general medical history, obstetric history (miscarriage; defined as a non vital intra-uterine pregnancy diagnosed before a GA of 16 weeks, preterm delivery; defined as GA < 32 weeks, hypertensive disorders; pre-existent hypertension, gestational hypertension, pre-eclampsia, eclampsia and HELLP-syndrome; Gestational hypertension was diagnosed if the following criteria were met: systolic blood pressure ≥ 140 mmHg and/ or diastolic blood pressure ≥ 90mmHg from a GA of 20 weeks and onwards in women with previously normal blood

pressure. Pre-eclampsia was defined as a combination of gestational hypertension with proteinuria (≥ 300mg/ 24 hours). Eclampsia was defined as a combination of the pre-eclampsia criteria and the presence of seizures.[15] The diagnosis HELLP syndrome was made when the following laboratory abnormalities were present: AST > 70 U/L, ALT > 70 U/L, LDH > 600 U/L, platelet count < 100x 10^9/L and evidence of haemolysis.[16] The presence of pre-existent hypertension was recorded if the gestational hypertension criteria were met before a GA of 20 weeks. Intra-uterine growth restriction (IUGR; defined as birth weight <p10), perinatal deaths, placental abruption; diagnosed clinically and was confirmed by the presence of an impression (and blood clot) on the maternal placental side)[17], placenta praevia; diagnosed by transvaginal ultrasonography in case the placenta was found to cover (completely or partially) the internal ostium of the cervix[18] and gestational diabetes; defined as glucose intolerance with onset or first recognition during pregnancy. Gestational diabetes was diagnosed in case of a fasting glucose of > 7.0mmol/l or abnormal oral glucose tolerance test[19]) and obstetric complications in the index pregnancy. These complications included extreme IUGR (defined as birth weight <p2.3), fetal distress (defined as CTG abnormalities according to the FIGO guidelines[20]), intra-uterine death, antepartum haemorrhage (placenta praevia, placental abruption, and vaginal bleeding with unknown cause in all trimesters), hypertensive disorders; thrombosis (either deep venous thrombosis (DVT) or pulmonary embolism (PE); DVT was defined as a partial or complete obliteration of a vein in the leg by a thrombus and was diagnosed by means of a Doppler examination. PE was defined as a partial or complete obliteration of a pulmonary artery by an embolus and was diagnosed by means of a spiral CT scan[21]), gestational diabetes, twin-to-twin transfusion syndrome; defined according to Quintero[22], preterm labour (defined as spontaneous onset of contractions resulting in cervical dilation at a GA < 32 weeks), preterm premature rupture of membrane (PPROM, before onset of labour and confirmed by a positive fern test), intra-uterine infection (diagnosed on histopathology of the placenta) and cord prolapse. Medication used during pregnancy was recorded as well. The mode of delivery and the indication for caesarean section were recorded. GA was based on the last menstrual period and an ultrasound examination. SGA infants were defined as a birth weight percentile < p10. Birth weight percentiles were determined according to the data of the Perinatal Registry of the Netherlands.[23] Mortality and time of death were recorded. The primary cause of death was determined according to clinical signs and/ or post-mortem investigations.

The data were analysed for the total cohort (infants delivered in a ten year study period between 1996 and 2005) as well as for cohort I (infants delivered between 1996 and 2000) and cohort II (infants delivered between 2001 and 2005). The reason for the comparison of both five year birth periods was to analyze possible differences over time.

Statistical analysis

To check for accuracy, the data entered were double checked. All analyses were performed by using SPSS version 15.0. Statistical comparisons for continuous variables were made with Mann- Whitney tests, and for comparisons of categorical variables a Chi-square test was performed. A Fisher's exact test was used instead of a Chi-square test when frequencies were small, resulting in ≥ 25% of the expected values less than 5. A *p* value of < 0.05 was considered to be statistically significant.

Results

Characteristics of the total cohort

Table 1. shows the characteristics of the total cohort (n=261, delivered between 1996 and 2005), cohort I (n=145, delivered in 1996 through to 2000) and cohort II (n=116, delivered in 2001 through to 2005), AGA infants (≥ p10, n=95) and SGA infants (< p10, n=166). The mean birth weight of the total cohort was 603g (SD 124g) and the mean GA 27.6 weeks (SD 2.6 weeks). No significant differences were noted between the two cohorts except for a significantly higher birth weight in cohort II (619 versus 591g in cohort I, *p*=0.017). There was no significant difference in the number of SGA infants born in the two consecutive five year study periods.

According to the definition a significantly shorter GA was found in the AGA infants (26.3 versus 28.3 weeks in SGA, *p* <0.001) and a significantly lower birth weight was found for the SGA infants (555 versus 689g in AGA, *p* <0.001). The majority of the SGA infants were male gender (50% versus 33.7% in AGA, *p*=0.014).

Obstetric history of the multigravids

Table 2. shows the obstetric history of the multigravids (n=121). A complicated obstetric history was noted in 84.3% of the multigravids; a previous miscarriage (1 or 2 times) occurred in 38%, 22.3% had a history of a preterm delivery, hypertensive disorders had occurred in 16.5%, 15.7% previously delivered a child with IUGR, and in 14.0% of the multigravids an intra-uterine death had occurred. Apart from a significantly higher prevalence of hypertensive disorders in cohort II (25.5% versus 10.0% in cohort I, *p*=0.023) there were no significant differences in obstetric history between the two cohorts. There were also no significant differences in the obstetric history of the multigravid mothers when comparing AGA and SGA infants.

Table 1. Characteristics of total cohort, cohort I and cohort II, AGA and SGA infants.

	Total cohort n=261	Cohort I n=145	Cohort II n=116	Cohort I vs II	AGA n=95	SGA n=166	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Maternal characteristics							
- Mean (SD) maternal age (years)	30.3 (±5.5)	30.3 (±5.3)	30.4 (±5.7)	0.843	30.4 (±5.1)	30.3 (±5.7)	0.866
- Mean (SD) birth weight (gram)	603.4 (±123.5)	591.4 (±120.9)	618.5 (±125.5)	**0.017**	688.5 (±54.5)	554.8 (±125.6)	**<0.001**
- Mean (SD) gestational age (weeks)	27.6 (±2.6)	27.4 (±2.4)	27.8 (±2.7)	0.187	26.3 (±1.3)	28.3 (±2.8)	**<0.001**
- Primigravid	140 (53.6)	75 (51.7)	66 (56.0)	0.488	49 (51.6)	91 (54.8)	0.699
- Pre-existent hypertension	39 (14.9)	17 (11.7)	22 (19.0)	0.117	29 (17.5)	10 (10.5)	0.151
- Diabetes	1 (0.4)	0	1 (0.9)	1.000	1 (1.1)	0	0.364
- Renal disease	4 (1.5)	3 (2.1)	1 (0.9)	0.631	1 (1.1)	3 (1.8)	1.000
Neonatal characteristics							
- Multiple birth	55 (21.1)	31 (21.4)	24 (20.7)	0.892	24 (25.3)	31 (18.7)	0.269
- Male gender	115 (44.1)	64 (44.1)	51 (44.0)	0.978	32 (33.7)	83 (50.0)	**0.014**
- SGA	166 (63.6)	97 (66.9)	69 (59.5)	0.245	-	-	-

Total cohort: born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005. AGA: appropriate for gestational age ≥ p10, SGA: small for gestational age < p10. SD: standard deviation.

Table 2. Obstetric history of multigravids of total cohort, cohort I and cohort II, AGA and SGA infants.

	Multigravids Total cohort n= 121	Multigravids Cohort I n= 70	Multigravids Cohort II n= 51	Cohort I vs II	Multigravids AGA n= 46	Multigravids SGA n= 75	AGA vs SGA
Obstetric history	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Uncomplicated obstetric history	19 (15.7)	11 (15.7)	8 (15.7)	0.997	5 (10.9)	14 (18.7)	0.310
Miscarriage 1 or 2	46 (38.0)	27 (38.6)	19 (37.3)	0.883	20 (43.5)	26 (34.7)	0.343
Miscarriage ≥ 3	10 (8.3)	6 (8.6)	4 (7.8)	1.000	3 (6.5)	7 (9.3)	0.740
Preterm delivery (GA < 32 weeks)	27 (22.3)	17 (24.3)	10 (19.6)	0.542	13 (28.3)	14 (18.7)	0.263
Hypertensive disorders	20 (16.5)	7 (10.0)	13 (25.5)	**0.023**	8 (17.4)	12 (16.0)	1.000
IUGR (birth weight < p10)	19 (15.7)	9 (12.9)	10 (19.6)	0.314	7 (15.2)	12 (16.0)	1.000
Intra-uterine death	17 (14.0)	7 (10.0)	10 (19.6)	0.133	5 (10.9)	12 (16.0)	0.592
Neonatal death	4 (3.3)	2 (2.9)	2 (3.9)	1.000	1 (2.2)	3 (4.0)	1.000
Placental abruption	2 (1.7)	1 (1.4)	1 (2.0)	1.000	0	2 (2.7)	0.525
Placenta praevia	0	0	0	-	0	0	-
Gestational diabetes	1 (0.8)	1 (1.4)	0	1.000	0	1 (1.3)	1.000

Total cohort: born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥ p10, SGA: small for gestational age < p10, hypertensive disorders: gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome, IUGR: intra-uterine growth restriction.

Obstetric complications during pregnancy

Table 3. shows the obstetric complications which occurred during the 261 pregnancies studied. The most prevalent complication was a hypertensive disorder in 136 (52.1%) women. In the majority pre-eclampsia was present (72.8%) and HELLP syndrome developed in 53.7%. 85.3% of the women who experienced a hypertensive disorder during the pregnancy required treatment with antihypertensive medication. Presence of a hypertensive disorder was more common in cohort II (62.9% versus 43.4% in cohort I, p=0.002), as well as gestational hypertension (23.3% versus 9.5% in cohort I, p=0.040). Whereas HELLP- syndrome developed significantly more often in cohort I (65.1% versus 43.8% in cohort II, p=0.016). As expected hypertensive disorders were also more common in SGA infants (58.4% versus 41.1% in AGA, p=0.007).

In the total cohort fetal distress occurred in 39.5% and an intra-uterine death rate of 35.2% was found. A significantly higher prevalence of intra-uterine deaths was found in SGA infants (44.0% versus 20% in AGA, p <0.001). In the total cohort extreme IUGR (birth weight < p2.3) occurred in 32.6%, and indeed only in SGA infants (51.2%). Spontaneous preterm labour (GA < 32 weeks) occurred in 28% of the infants, and was more common in AGA infants (50.5% versus 15.1% in SGA, p <0.001). PPROM occurred in almost 16% of the total cohort and was also more common in AGA infants (30.5% versus 7.2% in SGA, p=0.001). An intra-uterine infection was significantly more prevalent in AGA infants (14.7% versus 1.2% in SGA, p <0.001).

Intra-uterine deaths

In Table 4. the cause of death of the intra-uterine deaths is shown. The majority of infants died due to placental insufficiency (59.8%) and a substantial part (23.9%) resulted from termination of pregnancy because of a severe and deteriorating maternal condition due to pre-existent hypertension, gestational hypertension, (pre) eclampsia or HELLP syndrome. No significant differences were noted between the causes of death in the two cohorts. Whereas comparison of AGA and SGA infants showed that significantly more SGA infants died due to normotensive placental insufficiency (30.1% versus 5.3% in AGA infants, p=0.035), and significantly more AGA infants due to an intra-uterine infection (26.3% versus 1.4% in SGA infants, p=0.001).

Table 3. Obstetric complications of index pregnancies total cohort, cohort I and cohort II, AGA and SGA infants.

Obstetric complications index pregnancy	Total cohort n=261 n (%)	Cohort I n=145 n (%)	Cohort II n=116 n (%)	Cohort I vs II p-value	AGA n=95 n (%)	SGA n=166 n (%)	AGA vs SGA p-value
Hypertensive disorders	136 (52.1)	63 (43.4)	73 (62.9)	**0.002**	39 (41.1)	97 (58.4)	**0.007**
-pre-existent hypertension	39 (28.7)	17 (27.0)	22 (30.1)	0.708	10 (25.6)	29 (29.9)	0.680
-gestational hypertension	23 (16.9)	6 (9.5)	17 (23.3)	**0.040**	6 (15.4)	17 (17.5)	0.808
-pre-eclampsia	99 (72.8)	50 (79.4)	49 (67.1)	0.125	31 (79.5)	68 (70.1)	0.295
-HELLP syndrome	73 (53.7)	41 (65.1)	32 (43.8)	**0.016**	24 (61.5)	49 (50.5)	0.261
-eclampsia	5 (3.7)	4 (6.3)	1 (1.4)	0.182	1 (2.6)	4 (4.1)	1.000
Fetal distress	103 (39.5)	56 (38.6)	47 (40.5)	0.755	31 (32.6)	72 (43.4)	0.114
Intra-uterine death	92 (35.2)	56 (38.6)	36 (31.0)	0.202	19 (20.0)	73 (44.0)	**<0.001**
IUGR (birth weight < p2.3)	85 (32.6)	48 (33.1)	37 (31.9)	0.895	0	85 (51.2)	**<0.001**
Preterm labour (GA < 32 weeks)	73 (28.0)	44 (30.3)	29 (25.0)	0.405	48 (50.5)	25 (15.1)	**<0.001**
PPROM (GA < 32 weeks)	41 (15.7)	25 (17.2)	16 (13.8)	0.496	29 (30.5)	12 (7.2)	**0.001**
Intra-uterine infection	16 (6.1)	7 (4.8)	9 (7.8)	0.327	14 (14.7)	2 (1.2)	**<0.001**
Vaginal bleeding 1st & 2nd trimester	15 (5.7)	11 (7.6)	4 (3.4)	0.154	4 (4.2)	11 (6.6)	0.583
Vaginal bleeding 3rd trimester	29 (11.1)	19 (13.1)	10 (8.6)	0.252	13 (13.7)	16 (9.6)	0.413
Placental abruption	14 (5.4)	7 (4.8)	7 (6.0)	0.667	6 (6.3)	8 (4.8)	0.776
Placenta praevia	2 (0.8)	1 (0.7)	1 (0.9)	1.000	1 (1.1)	1 (0.6)	1.000
Thrombosis	0	0	0	-	0	0	-
Gestational diabetes	0	0	0	-	0	0	-
Twin-to-twin transfusion syndrome	9 (3.4)	6 (4.1)	3 (2.6)	0.735	5 (5.3)	4 (2.4)	0.293
Cord prolapse	2 (0.8)	1 (0.7)	1 (0.9)	1.000	2 (2.1)	0	0.132

Total cohort: born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥ p10, SGA: small for gestational age < p10, IUGR: intra- uterine growth restriction, hypertensive disorders: gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome, Thrombosis: deep venous thrombosis and pulmonary embolism, PPROM: preterm premature rupture of membrane.

Table 4. Intra-uterine deaths: cause of death.

	Total n=92	Cohort I n=56	Cohort II n=36	Cohort I vs II	AGA n=19	SGA n=73	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Hypertensive placental insufficiency	32 (34.8)	16 (28.6)	16 (44.4)	0.178	4 (21.1)	28 (38.4)	0.187
Normotensive placental insufficiency	23 (25.0)	15 (26.8)	8 (22.2)	0.806	1 (5.3)	22 (30.1)	**0.035**
Placental abruption	3 (3.3)	1 (1.8)	2 (5.6)	0.559	2 (10.5)	1 (1.4)	0.107
Termination of pregnancy for severe maternal condition*	22 (23.9)	13 (23.2)	9 (25.0)	0.800	5 (26.3)	17 (23.3)	0.769
Intra-uterine infection	6 (6.5)	6 (10.7)	0	0.078	5 (26.3)	1 (1.4)	**0.001**
Twin-to-twin transfusion syndrome	6 (6.5)	5 (8.9)	1 (2.8)	0.398	2 (10.5)	4 (5.5)	0.600

Total cohort: born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005. AGA: appropriate for gestational age ≥ p10, SGA: small for gestational age < p10, *severe maternal condition: deteriorating maternal condition due to pre-existent hypertension, gestational hypertension, (pre)eclampsia or HELLP syndrome.

Mode of delivery

Table 5. shows the mode of delivery. 50 (19.2%) infants were delivered by spontaneous vaginal delivery. These were preterm deliveries in which tocolysis failed or was discontinued because of the fetal condition or a suspected intra-uterine infection. Induction of vaginal delivery occurred in the majority because of intra-uterine death, or due to severe maternal complications and doubtful viability of the fetus.

A caesarean section was performed in 47.9%. The majority of infants in which the fetal prognosis was judged to be worthwhile were delivered by caesarean section. A caesarean section was performed in 72.8% because of fetal distress, and in 18.4% because of a deteriorating maternal condition due to pre-existent hypertension, gestational hypertension, (pre)eclampsia or HELLP syndrome. Comparison of cohort I and II showed no significant difference in the prevalence of caesarean sections (45.5% and 50.9%, p=0.390).

Significantly more AGA infants were born after spontaneous vaginal delivery (70.7% versus 11.5% in SGA, p <0.001), whereas induction because of intra-uterine death significantly more often occurred in SGA infants (61.5% versus 20.7% in AGA, p <0.001). Also significantly more SGA infants were born after induction because of a deteriorating maternal condition (26.9% versus 6.9% in AGA, p=0.003).

The majority of caesarean sections performed for AGA as well as SGA infants was because of fetal distress. Nevertheless, fetal distress was a significantly more common indication for caesarean section in SGA infants (79.5% versus 56.8% in AGA, p=0.015). Whereas, in AGA infants a caesarean section was significantly more often performed for maternal indication (35.1% versus 11.4% in SGA, p=0.003).

Survival

Of the 261 pregnancies, 169 (64.8%) pregnancies have resulted in the birth of a live born infant. In Table 6. the outcome of these infants is shown. 29 infants (17.2%) died in the delivery room, the majority died because no intensive care was initiated in view of extreme prematurity. 35 infants (20.7%) died in the NICU, the majority of infants died after withdrawal of intensive care because of severe cardiorespiratory failure and cerebral lesions. 105 infants (62.1%) survived to discharge from the NICU, and none of them died after discharge. No significant differences in survival were noted between both cohorts and AGA and SGA infants (56.2% and 68.8%, p=0.113 and 57.9% and 65.6%, p=0.341 respectively).[24]

Table 5. Mode of delivery.

	Total cohort n=261	Cohort I n=145	Cohort II n=116	Cohort I vs II	AGA n=95	SGA n=166	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Vaginal delivery	136 (52.1)	79 (54.5)	57 (49.1)	0.455	58 (61.1)	78 (47.0)	**0.039**
- spontaneous delivery	50 (36.8)	26 (32.9)	24 (42.1)	0.286	41 (70.7)	9 (11.5)	**<0.001**
- forceps	1 (0.7)	0	1 (1.8)	0.419	1 (1.7)	0	0.426
- induction because of intra-uterine death	60 (44.1)	42 (53.2)	18 (31.6)	**0.015**	12 (20.7)	48 (61.5)	**<0.001**
- induction for severe maternal condition	25 (18.4)	11 (13.9)	14 (24.6)	0.123	4 (6.9)	21 (26.9)	**0.003**
Caesarean section	125 (47.9)	66 (45.5)	59 (50.9)	0.390	37 (38.9)	88 (53.0)	**0.039**
- fetal distress	91 (72.8)	53 (80.3)	38 (64.4)	0.069	21 (56.8)	70 (79.5)	**0.015**
- maternal condition	23 (18.4)	9 (13.6)	14 (23.7)	0.170	13 (35.1)	10 (11.4)	**0.003**
- both maternal and fetal reasons	5 (4.0)	2 (3.0)	3 (5.1)	0.666	3 (8.1)	2 (2.3)	0.153
- intra-uterine death but other of multiple pregnancy alive	6 (4.8)	2 (3.0)	4 (6.8)	0.420	0	6 (6.8)	0.178

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥ p10, SGA: small for gestational age < p10, maternal condition: severe and deteriorating pre-existent hypertension, gestational hypertension, (pre)eclampsia, HELLP syndrome. Fetal reasons: fetal distress and/ or severe IUGR.

Table 6. Outcome of the 169 pregnancies which resulted in live born infants.

	Total cohort n=169	Cohort I n=89	Cohort II n=80	Cohort I vs II	AGA n=76	SGA n=93	AGA vs SGA
Outcome	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Died in delivery room	29 (17.2)	12 (13.5)	17 (21.3)	**0.004**	15 (19.7)	14 (15.1)	0.603
Died in NICU	35 (20.7)	27 (30.3)	8 (10.0)		17 (22.4)	18 (19.4)	
Alive at discharge	105 (62.1)	50 (56.2)	55 (68.8)		44 (57.9)	61 (65.6)	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, NICU: neonatal intensive care unit.

Discussion

Women who delivered an infant with a birth weight ≤ 750g have a considerable prevalence of hypertension in their general medical history. The multigravids of our maternal study population almost invariably had a complicated obstetric history, with a high prevalence of repeated miscarriages, preterm delivery, IUGR, intra-uterine death and hypertensive disorders such as pre-existent hypertension, gestational hypertension, (pre)eclampsia and HELLP syndrome (Table 2).

The index pregnancy was largely characterised by complications of placental origin: mainly placental insufficiency accompanied by hypertensive disorders. This resulted in a high prevalence of IUGR; birth weight below the 10th centile in 63.6% and below the 2.3rd centile in 32.6% and an intra-uterine death rate of over one third. The majority of the intra-uterine deaths were SGA infants and resulted as expected from placental insufficiency. Possibly the higher prevalence of male infants in the SGA cohort may have influenced the number of intra-uterine deaths. As from other studies it is known that female infants have a better chance of survival compared to their male peers.[25]

Hypertensive disorders were seen in about half the cases (pre-eclampsia and HELLP syndrome were most commonly found) and a significantly higher prevalence of hypertensive disorders was found in cohort II and SGA infants. Vohr et al. showed that increased maternal age is related to the occurrence of hypertensive disorders.[26] Hargood and Dukler reported an increased risk of pre-eclampsia in primigravids.[8,10] Since no significant differences in maternal age and the number of primigravids between cohort I and II were found, the higher prevalence of hypertensive disorders in the obstetric history of women in cohort II appears to be predictive for the significantly higher percentage of hypertensive disorders in the index pregnancies in cohort II.

The significantly higher birth weight in cohort II could not be explained. According to the definition a significantly higher birth weight and shorter gestational age was found in AGA infants.

The significantly higher presence of intra-uterine infections in AGA infants can be explained from the higher prevalence of PPROM.

Well known is that fetal growth restriction due to placental insufficiency may result in fetal distress. In our SGA infants the high prevalence of (extreme) intrauterine growth restriction resulted in a significantly higher prevalence of fetal distress as indication for caesarean section, compared to AGA infants.

The higher prevalence of caesarean sections for a deteriorating maternal condition due to hypertensive disorders was unexpectedly noted in AGA infants. However, because the greater part of the SGA infants were delivered by caesarean section because of fetal distress, the higher prevalence of caesarean sections for maternal condition in AGA infants is explainable by the small remaining number of SGA infants for other indications.

Multiple pregnancies were over-represented in cohort I and II as well as in SGA and

AGA infants. 21.1% of the infants with a birth weight ≤ 750g were part of a twin or triplet pregnancy (Table 1).
Due to a high prevalence of placental insufficiency, a substantial part of the infants were delivered by caesarean section (almost 50%), largely due to fetal distress and severe maternal morbidity. Infants with a birth weight ≤ 750g born after spontaneous preterm birth occurred in a minority (almost 20%). Against this background we can question whether the birth of an infant with a birth weight ≤ 750g can be prevented. Most of our cases were associated with placental disorders but this is not yet accessible to an effective therapy. Low dose of acetylsalicyl acid starting early in pregnancy in women with a history of pre-eclampsia and placental insufficiency has been shown to result in a minor reduction of this complication.[27]
High dose of vitamin C and E at first seemed to reduce the incidence of pre-eclampsia as well, but a large randomised placebo controlled trial showed no effect.[28] Women with HELLP-syndrome experimentally treated with steroids also showed no beneficial effect on pregnancy outcome (maternal and perinatal mortality, major maternal and perinatal morbidity).[29] However, biochemical markers combined with flow measurements of uterine arteries early in pregnancy may predict pre-eclampsia and placental insufficiency later in pregnancy, but as mentioned before an effective therapy is as yet not available.[30] In women with a history of early preterm birth prophylactic administration of progesterone significantly reduced the risk of delivery at less than 34 and 37 weeks of gestation according to a Cochrane review of Dodd et al.[31] In artificial reproduction the increased risk of multiple pregnancies is well known, still the aim is to keep the number of multiple pregnancies as low as possible. Furthermore general measures as cessation of smoking, alcohol and drugs are important to prevent intra-uterine growth restriction.[32,33] However, all these measures may only result in a minor reduction of infants with a birth weight ≤ 750g.
In conclusion, a high percentage of parous mothers already had serious complications in their obstetric history. The index pregnancy of both parous and nulliparous women was largely complicated by hypertension, preeclampsia and/or HELLP syndrome. The majority of the children born with a birth weight ≤ 750g are growth restricted due to placental insufficiency caused by hypertensive disorders of their mother, resulting in a high percentage of caesarean sections. Only a minority of the children ≤ 750g at birth are not growth restricted and are born after spontaneous vaginal delivery accompanied in about one third by PPROM. 62.1% of the 169 live born ELBW infants survived, however these infants remain very vulnerable. Especially since the majority of these ELBW children are not only born extremely preterm but also growth restricted, follow-up studies are extremely important to evaluate neonatal morbidity and neurodevelopmental outcome. In future publications the follow-up at 2, 3.5 and 5 years of age of this cohort of ELBW infants will be reported.

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4

Changes in survival and neonatal morbidity in infants with a birth weight ≤ 750 gram

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Abstract

Background: Improvement in perinatal and neonatal care has resulted in increased survival of extremely low birth weight (ELBW) infants.

Objectives: To describe survival and neonatal morbidity in a cohort of ELBW infants, to compare two consecutive 5-year periods, and compare appropriate (AGA) with small for gestational age (SGA) infants (AGA: ≥p10, and SGA: <p10).

Methods: Retrospective cohort study of 179 live-born infants with a birth weight (BW) of ≤750 g and gestation of ≥24 weeks, born in 1996–2000 (cohort I, n = 94) and 2001–2005 (cohort II, n = 85) in the Wilhelmina Children's Hospital Utrecht, the Netherlands.

Results: During NICU stay (n = 146) 62.3% experienced infant respiratory distress syndrome (IRDS), 46.6% bronchopulmonary dysplasia, 50.7% septicemia, 34.2% periventricular leukomalacia grade I and 24.7% intraventricular hemorrhage grade I/II. IRDS grade III/IV occurred significantly more often in cohort I ($p = 0.042$), whereas septicemia and hyperbilirubinemia occurred more in cohort II ($p = 0.045$ and $p = 0.001$). In AGA infants mean gestation was significantly shorter ($p < 0.001$), and IRDS grade III/IV ($p = 0.015$), mechanical ventilation ($p = 0.045$) and patent ductus arteriosus ($p = 0.003$) were significantly more prevalent. Overall survival was 62%, and survival in the NICU increased from 65.8% (cohort I) to 88.1% (cohort II, $p = 0.002$). Survival of AGA and SGA infants did not differ, but increased with time (71.4 to 75.9% and 61.4 to 97.4%, respectively).

Conclusions: Mortality of infants with a BW of ≤750 g is high, but decreased over time, especially in SGA infants. Considerable neonatal morbidity was present, especially in AGA infants, most likely due to their significantly shorter gestation.

Introduction

Advances in perinatal and neonatal care resulted in an increased survival rate of extremely (ELBW, birth weight <1000 g) and very low birth weight infants (VLBW, <1500 g) as well as extremely preterm infants (gestational age <26 weeks).[1-6] However in these neonates a high prevalence of serious neonatal morbidities, such as hypotension, cerebral lesions, sepsis, necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD) is found.[7-9] Regev et al.[10] showed that SGA infants are at increased risk of death, BPD and retinopathy of prematurity. Bernstein et al.[11] showed an increased risk of neonatal death, infant respiratory distress syndrome (IRDS) and NEC in infants with a birth weight (BW) of 501–1500g. To a certain degree low BW and prematurity together with the complications experienced in the neonatal period explain the subsequent neurodevelopmental outcome. For this reason these infants remain at high risk of neurodevelopmental impairments such as cognitive delay, cerebral palsy, blindness and deafness.[1-3,6,12,13]

Thorough knowledge of morbidity, survival and neurodevelopmental outcome of ELBW infants is required in order to make well-balanced decisions regarding the care of these infants by the attending obstetrician and neonatologist together with the parents.

The objectives of this retrospective cohort study of 179 live-born infants with a BW of ≤750 g were threefold. Firstly, to assess neonatal morbidity during neonatal intensive care unit (NICU) stay and survival rates of the infants born during a 10-year study period. Secondly, to compare survival and neonatal morbidity between two consecutive 5-year study periods. Thirdly, to analyze possible differences in neonatal morbidity and survival between appropriate for gestational age (AGA, ≥p10) infants and small for gestational age (SGA, <p10).

Subjects and Methods

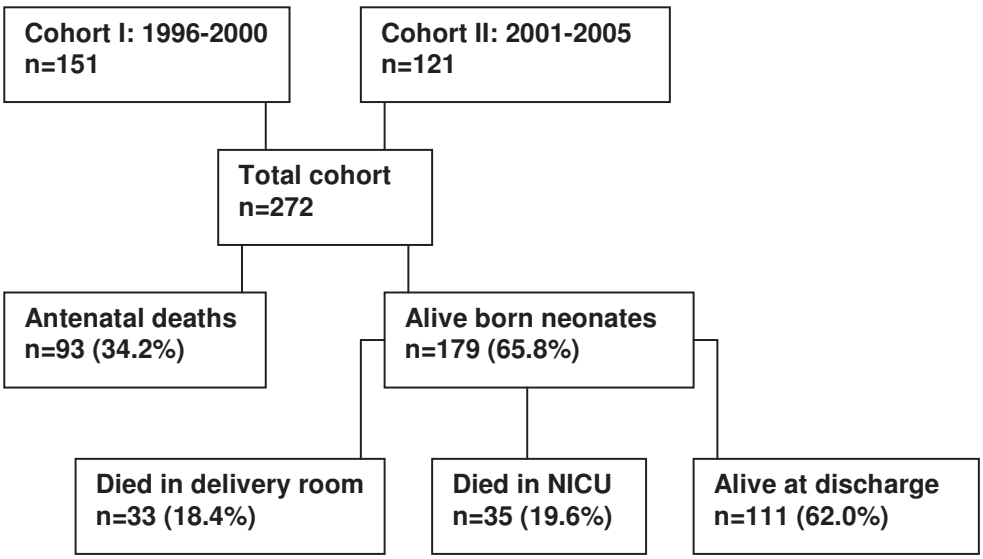
All neonates with a BW of 750 g or less and a gestational age (GA) of at least 24 completed weeks, born in 1996–2000 (cohort I, n = 151) and 2001–2005 (cohort II, n = 121) in the Wilhelmina Children's Hospital in Utrecht, the Netherlands, were eligible for this study. Neonates who were born at 24 completed weeks or more, but who died in utero before 24 completed weeks were excluded. Also infants with congenital or chromosomal disorders were excluded.

Our study population consisted of 272 infants, of these infants 93 (34.2%) were intrauterine deaths [unpublished data] and 179 (65.8%) live-born infants (Figure 1).

Details of Ethics Approval

The parents of all patients admitted to our University Medical Centre gave consent for the use of their data for scientific research, and also agreed to participate in the neonatal follow-up program of the Wilhelmina Children's Hospital. These data were processed anonymously.

Figure 1. Cohort of 272 infants with a birth weight ≤ 750g born in 1996-2005.



Data Collection and Definitions

Maternal and neonatal data were collected by reviewing the medical charts and were entered in the dataset. Mode of delivery and indication for cesarean section were recorded. GA was based on the last menstrual period and early ultrasound examination. BW percentiles were determined according to the data of the Perinatal Registry of the Netherlands.[14] SGA was defined as infants with a BW percentile of <p10.

In our hospital the policy to initiate intensive care for very preterm infants is based on the following criteria: intensive care was generally not offered to infants with a GA of 24 weeks or born at 25 weeks but presenting with perinatal asphyxia or severe respiratory problems at delivery. We specified perinatal asphyxia and severe respiratory problems as a very poor condition at birth presenting as a neonate with bradycardia, without any effort of spontaneous breathing, and not responding to bag and mask ventilation. Infants with a GA of 24 weeks were only admitted when they were doing well at birth, and not immediately requiring artificial ventilation. The number of infants with a GA of 24 weeks admitted to our NICU is therefore limited. Intensive care was offered to infants born at 25 weeks without perinatal asphyxia or severe respiratory problems, and intensive care was always offered to infants with a GA of 26 weeks.

Mortality and time of death were recorded. The primary cause of death was determined according to clinical signs and/or post-mortem investigations. The infants who died during NICU stay either died following withdrawal of intensive care because of

severe cardiorespiratory failure, or a combination of severe cardiorespiratory failure and severe cerebral lesions or the presence of severe cerebral lesions exclusively.
Severe cardiorespiratory failure was defined as the impossibility to continue mechanical ventilation because of the need for very high pressures, associated with the presence or development of severe pulmonary damage on chest X-ray. The second major reason for withdrawal of intensive care was a combination of severe cardiorespiratory failure and severe cerebral lesions. These severe cerebral lesions were defined as intraventricular hemorrhage grade III with severe acute ventricular dilatation of the lateral ventricles or a large unilateral grade IV or bilateral grade IV hemorrhage.
Admission to the NICU was divided into short-term (≤28 days) or long-term (>28 days) stay. Mechanical ventilation was recorded as short-term (<2 weeks), intermediate (2–4 weeks) or long-term (>4 weeks). No subdivision was made between intermittent positive pressure ventilation and high frequency oscillatory ventilation (HFOV). Oxygen requirement was also recorded. IRDS grades I–IV were defined according to Giedion et al.[15] BPD was defined as the need for oxygen at 36 weeks according to Shennan et al.[16] Antenatal betamethasone and postnatal hydrocortisone use was registered. Hypotension was defined according to postnatal age-specific blood pressure standards and treatment with inotropes was registered. Patent ductus arteriosus (PDA) was diagnosed clinically and confirmed by cardiac ultrasound. Treatment of PDA with indomethacin or surgery was recorded.
Periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH) were graded according to de Vries et al.[17] Septicemia was defined as clinical signs in combination with a positive blood culture. NEC was classified according to the criteria of Bell et al.[18] Conservative or surgical treatment for NEC was recorded. Hyperbilirubinemia was registered as needing phototherapy according to postnatal age-specific bilirubin levels.[19] Hypothyroidism was diagnosed according to postnatal age-specific standards for free T4 and TSH.[20] Definitions used for hypoglycaemia and hyperglycemia, according to the perinatal registry of the Netherlands, were a plasma glucose of <2.6 mmol/l and a glucose of >8.0 mmol/l.[21]

Statistical Analysis
To check for accuracy, data entered were double checked. All analyses were performed using SPSS version 15.0. Statistical comparisons for continuous variables were made with independent t tests or Mann-Whitney tests, and for comparisons of categorical variables a Chi-square test was performed. A Fisher's exact test was used instead of Chi-square test when frequencies were small, resulting in ≥25% of the expected values less than 5. A p value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

Table 1 shows the characteristics of all live-born infants (n = 179) born between 1996 and 2005, cohort I (n = 94, born between 1996 and 2000) and cohort II (n = 85, born between 2001 and 2005), AGA and SGA infants. The mean BW of the total cohort was 641 (SD 93) g and the mean GA 27.50 (SD 2.1) weeks. No significant differences were noted between the two cohorts except for a significantly higher BW in cohort II (664 versus 621 g, $p = 0.001$). There was no significant difference in the number of SGA (<p10) and AGA (≥p10) infants between the two cohorts ($p = 0.385$). A significantly shorter GA was found in the AGA infants (26.30 versus 28.49 weeks, $p < 0.001$) and a significantly lower BW was found for the SGA infants (595 vs. 697 g, $p < 0.001$). The majority of the SGA infants were male gender (51.0 vs. 33.3% of AGA infants, $p = 0.023$), whereas significantly more AGA infants were part of a multiple pregnancy (30.9 vs. 15.3%, $p = 0.019$).

Mode of Delivery

Table 2 shows the mode of delivery of the 179 infants. Almost one third of the infants were born by vaginal delivery, and the majority was born by spontaneous vaginal delivery. These were preterm deliveries in which tocolysis failed or was discontinued because of the fetal condition or a suspected intrauterine infection.

A cesarean section was the mode of delivery in 68.7%. The major indications were fetal distress in 77.2%, and a severe and deteriorating maternal condition due to preeclampsia, eclampsia or HELLP syndrome in 18.7%. There were no significant differences in the mode of delivery between cohorts I and II.

Comparison of AGA and SGA infants showed a significantly higher percentage of cesarean sections in SGA infants (86.7 vs. 46.9%, $p < 0.001$). The majority of cesarean sections performed for AGA as well as for SGA infants was because of fetal distress (57.9 and 85.9%, $p = 0.001$). Whereas the maternal condition was significantly more often the reason for a cesarean section in AGA infants (34.2 vs. 11.8% in SGA infants, $p = 0.005$).

Neonatal Morbidity during NICU Stay

Of the 179 infants, 146 infants (81.6%) were admitted to the NICU. Table 3 shows the neonatal morbidity of these infants. More than two thirds needed to stay in NICU for more than 28 days. The majority (82.9%) required mechanical ventilation and of these infants 14.4% needed ventilatory support for more than 4 weeks. IRDS grades I/II and III/IV were diagnosed in more than one fourth and more than one third, respectively. The majority of the infants with IRDS received surfactant.

BPD developed in 46.6% and >65% of the BPD cases received hydrocortisone treatment. In 64.4% hypotension was present and the majority needed treatment with inotropes. PDA was diagnosed in one third of the infants, more than half of

Table 1. Characteristics of live born infants.

	Total cohort n=179	Cohort I n=94	Cohort II n=85	Cohort I vs II	AGA n=81	SGA n=98	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Mean maternal age (years, SD)	30.0 (±5.3)	29.9 (±5.1)	30.2 (±5.5)	0.738	29.8 (±5.0)	30.2 (±5.5)	0.387
Mean birth weight (gram, SD)	641 (±93)	621 (±96)	664 (±84)	**0.001**	697 (±46)	595 (±97)	**<0.001**
Mean gestational age (weeks, SD)	27.50 (±2.1)	27.45 (±2.0)	27.54 (±2.2)	0.861	26.30 (±1.3)	28.49 (±2.1)	**<0.001**
Primigravid	100 (55.9)	52 (55.3)	48 (56.5)	0.882	43 (53.1)	57 (58.2)	0.547
Multiple birth	40 (22.3)	20 (21.3)	20 (23.5)	0.724	25 (30.9)	15 (15.3)	**0.019**
Male	77 (43.0)	41 (43.6)	36 (42.4)	0.881	27 (33.3)	50 (51.0)	**0.023**
Prenatal steroids (GA < 32 weeks)	132 (76.7)	66 (73.3)	66 (80.5)	0.284	61 (77.2)	68 (75.6)	0.857
5–min Apgar score < 7	50 (27.9)	27 (28.7)	23 (27.1)	0.868	27 (33.3)	23 (23.5)	0.181
SGA	98 (54.7)	56 (59.6)	42 (49.4)	0.180	-	-	-

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, GA: gestational age, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, SD: standard deviation.

Table 2. Mode of delivery of live born infants.

	Total cohort n=179	Cohort I n=94	Cohort II n=85	Cohort I vs II	AGA n=81	SGA n=98	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Vaginal delivery	56 (31.3)	29 (30.9)	27 (31.8)	1.000	43 (53.1)	13 (13.3)	**<0.001**
- spontaneous delivery	50 (89.3)	26 (89.7)	24 (88.9)	1.000	42 (97.7)	8 (61.5)	**0.002**
- forceps	1 (1.8)	0	1 (3.7)	0.482	1 (2.3)	0	1.000
- induction for severe maternal condition	5 (8.9)	3 (10.3)	2 (7.4)	1.000	0	5 (38.5)	**<0.001**
Caesarean section	123 (68.7)	65 (69.1)	58 (68.2)	1.000	38 (46.9)	85 (86.7)	**<0.001**
- fetal condition	95 (77.2)	54 (83.1)	41 (70.7)	0.132	22 (57.9)	73 (85.9)	**0.001**
- maternal condition	23 (18.7)	9 (13.8)	14 (24.1)	0.169	13 (34.2)	10 (11.8)	**0.005**
- both maternal and fetal reasons	5 (4.1)	2 (3.1)	3 (5.2)	0.666	3 (7.9)	2 (2.4)	0.171

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, maternal condition: severe preeclampsia, eclampsia, HELLP syndrome, fetal condition: fetal distress.

them received indomethacin, 14.3% required surgical closure, spontaneous closure occurred in 22.4%, and in 6.1% no treatment was initiated because severe cerebral complications had resulted in the decision to discontinue intensive care.
Cranial ultrasound showed PVL grade I in one third, IVH grade I/II in one fourth of the infants, and severe intracranial lesions (IVH grade III/IV or PVL grade II) were found in almost 10%. Septicemia occurred in 50%,NEC was diagnosed in 8.9%, and the majority required a laparotomy. During their stay in the NICU some infants experienced problems with their glucose homeostasis (hypoglycemia in 19.9% and hyperglycemia in 26.0%) and hyperbilirubinemia needing phototherapy was found in almost 70%.
The need for and duration of mechanical ventilation significantly decreased between cohorts I and II (p = 0.023). In cohort II significantly more infants did not need mechanical ventilation at all (p = 0.046), and fewer infants required mechanical ventilation for more than 4 weeks (p = 0.008). A higher prevalence of IRDS grade III/IV was present in cohort I (p = 0.042). Whereas significantly more infants of cohort II experienced septicemia and hyperbilirubinemia (p = 0.045 and p = 0.001, respectively). Hypothyroidism was found significantly more often in cohort I (p = 0.031).
Septicemia developed in 63.4% of the infants who had been in the NICU for more than 28 days, compared to 22.2% of the infants who stayed in the NICU for less than 28 days (p < 0.001).
The majority of both SGA and AGA infants needed to stay in the NICU for more than 28 days.
A higher prevalence of IRDS grade III/IV was noticed in AGA infants (p = 0.015), and significantly more AGA infants required mechanical ventilation (p = 0.045). Furthermore a PDA was significantly more often diagnosed in AGA infants (p = 0.003).

Survival
Total Cohort
Table 4 shows that 33 infants (18.4%) died in the delivery room. In the majority active resuscitation was withheld or discontinued in view of extreme prematurity combined with the very poor condition of 18 infants (54.5%) or signs of severe infection at birth in 7 infants (21.2%). Furthermore 4 infants (12.1%) died due to termination of pregnancy because of a severe and deteriorating maternal condition due to preeclampsia and/or HELLP syndrome, 3 infants (9.1%) due to placental insufficiency and 1 infant (3%) due to twin-to-twin transfusion syndrome.
Of the 146 infants admitted to the NICU 35 (24.0%) died: 6 of these infants (17.1%) within 24 h; 18 (51.4%) within 2–7 days; 5 (14.3%) within 8–28 days, and 6 (17.1%) after 28 days of life. The majority of infants died after withdrawal of intensive care because of severe cardiorespiratory failure (n = 23, 65.7%), followed by a combination

Table 3. Neonatal morbidity and interventions during NICU admission.

	Total Cohort n= 146	Cohort I n=79	Cohort II n=67	Cohort I vs II	AGA n= 64	SGA n= 82	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
NICU admission > 28 days	101 (69.2)	51 (64.6)	50 (74.6)	0.189	41 (64.1)	60 (73.2)	0.280
Ventilation				**0.023**			0.050
- no	25 (17.1)	9 (11.4)	16 (23.9)		6 (9.4)	19 (23.2)	
- short < 2 weeks	50 (34.2)	26 (32.9)	24 (35.8)		20 (31.3)	30 (36.6)	
- intermediate 2-4 weeks	50 (34.2)	27 (34.2)	23 (34.3)		25 (39.1)	25 (30.5)	
- long > 4 weeks	21 (14.4)	17 (21.5)	4 (6.0)		13 (20.3)	8 (9.8)	
Oxygen	135 (92.5)	76 (96.2)	59 (88.1)	0.063	60 (93.8)	75 (91.5)	0.756
IRDS				0.122			**0.005**
- no	55 (37.7)	27 (34.2)	28 (41.8)		15 (23.4)	40 (48.8)	
- grade I/II	39 (26.7)	28 (22.8)	21 (31.3)		19 (29.7)	20 (24.4)	
- grade III/IV	52 (35.6)	34 (43.0)	18 (26.9)		30 (46.9)	22 (26.8)	
Surfactant for IRDS	69 (75.8)	38 (73.1)	31 (79.5)	0.480	38 (77.6)	31 (73.8)	0.807
BPD	68 (46.6)	42 (53.2)	26 (38.8)	0.083	31 (48.4)	37 (45.1)	0.740
- hydrocortisone for BPD	45 (66.2)[a]	29 (69.0)	16 (61.5)	0.602	19 (61.3)	26 (70.3)	0.454
- hydrocortisone for BPD & hypotension	10 (20.8)[b]	8 (28.6)	2 (10.0)	0.160	7 (30.4)	3 (12.0)	0.162
Hypotension	94 (64.4)	53 (67.1)	41 (61.2)	0.459	44 (68.8)	50 (61.0)	0.385
Treatment for hypotension				1.000			0.520
- inotropes	73 (77.7)[c]	41 (77.4)	32 (78.0)		32 (72.7)	41 (82.0)	
- inotropes & hydrocortisone	6 (6.4)[c]	3 (5.7)	3 (7.3)		3 (6.8)	3 (6.0)	
- iv fluids only	15 (16.0)[c]	9 (17.0)	6 (14.6)		9 (20.5)	6 (12.0)	

	Total Cohort n= 146	Cohort I n=79	Cohort II n=67	Cohort I vs II	AGA n= 64	SGA n= 82	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
PDA	49 (33.6)	26 (32.9)	23 (34.3)	0.857	30 (46.9)	19 (23.2)	**0.003**
Treatment for PDA				0.123			0.327
- no: discontinuation NICU	3 (6.1)[d]	1 (3.8)	2 (8.7)		2 (6.7)	1 (5.3)	
- spontaneous closure	11 (22.4)[d]	7 (26.9)	4 (17.4)		5 (16.7)	6 (31.6)	
- indomethacin	28 (57.1)[d]	17 (65.4)	11 (47.8)		20 (66.7)	8 (42.1)	
- surgery	7 (14.3)[d]	1 (3.8)	6 (26.1)		3 (10.0)	4 (21.1)	
PVL				0.152			0.179
- no	94 (64.4)	54 (68.4)	40 (59.7)		43 (67.2)	51 (62.2)	
- grade I	50 (34.2)	23 (29.1)	27 (40.3)		19 (29.7)	31 (37.8)	
- grade II	2 (1.4)	2 (2.5)	0		2 (3.1)	0	
IVH				0.825			0.099
- no	98 (67.1)	52 (65.8)	46 (68.7)		37 (57.8)	61 (74.4)	
- grade I/II	36 (24.7)	21 (26.6)	15 (22.4)		21 (32.8)	15 (18.3)	
- grade III/IV	12 (8.2)	6 (7.6)	6 (9.0)		6 (9.4)	6 (7.3)	
Septicemia	74 (50.7)	34 (43.0)	40 (59.7)	**0.045**	30 (46.9)	44 (53.7)	0.505
NEC	13 (8.9)	4 (5.1)	9 (13.4)	0.077	6 (9.4)	7 (8.5)	1.000
- surgery for NEC	11 (84.6)[e]	4 (100)	7 (77.8)	1.000	4 (66.7)	7 (100)	0.192
Hyperbilirubinemia	101 (69.2)	45 (57.0)	56 (83.6)	**0.001**	42 (65.6)	59 (72.0)	0.471
Hypoglycaemia	29 (19.9)	12 (15.2)	17 (25.4)	0.124	12 (18.8)	17 (20.7)	0.836
Hyperglycaemia	38 (26.0)	16 (20.3)	22 (32.8)	0.084	19 (29.7)	19 (23.2)	0.448
Hypothyroidism	6 (4.1)	6 (7.6)	0	**0.031**	1 (1.6)	5 (6.1)	0.231

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PDA: patent ductus arteriosus, no treatment of PDA: discontinuation NICU because of severe cerebral lesions. PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis. a: % of patients who suffered BPD, b: % of patients who suffered BPD and hypotension, c: % of patients who suffered hypotension, d: % of patients who suffered PDA, e: % of patients who suffered NEC.

of severe cardiorespiratory failure and severe cerebral lesions in 7 (20%) infants, and due to cerebral lesions in 5 (14.3%) infants (Appendix Table 1).
111 infants (76.0%) were discharged home, none of the infants died after discharge from the NICU.

Cohorts I and II

Fewer infants in cohort II died during their stay in the NICU, resulting in a significantly increased survival over time, from 65.8% in cohort I to 88.1% in cohort II ($p = 0.002$; table 4). In cohort II significantly fewer infants died after withdrawal of intensive care due to severe cardiorespiratory failure or severe cerebral lesions (8 versus 27 infants in cohort I, $p = 0.043$, Appendix Table 2). Significantly more infants died due to a combination of cardiorespiratory failure and cerebral lesions in cohort II (50 vs. 11.1% in cohort I, $p = 0.033$) and the majority of infants in cohort I died from cardiorespiratory failure (74.1%).

SGA and AGA Infants

Similar survival rates for AGA and SGA infants who had been admitted to the NICU were found (73.4 and 78.0%, $p = 0.561$). However, significantly more SGA infants died after 28 days of life (33.3% versus none of the AGA infants, $p = 0.019$). Among the SGA infants were significantly more male infants, however survival did not differ between male and female infants (76.6 and 75.6%, $p = 1.000$; data not shown).
Table 5 shows the outcome of live-born SGA and AGA infants between cohorts I and II. The survival of SGA infants significantly increased with time (61.4 to 97.4%, $p < 0.001$), whereas the survival of AGA infants remained unchanged (71.4 to 75.9%, $p = 0.780$).

Table 4. Outcome of live born infants.

Outcome	Total cohort n=179 n (%)	Cohort I n=94 n (%)	Cohort II n=85 n (%)	Cohort I vs II p-value	AGA n=81 n (%)	SGA n=98 n (%)	AGA vs SGA p-value
Died in delivery room	33 (18.4)	15 (16.0)	18 (21.2)	0.441	17 (21.0)	16 (16.3)	0.445
Admitted to NICU	146 (81.6)	79 (84.0)	67 (78.8)		64 (79.0)	82 (83.7)	
- Died in NICU	35 (24.0)	27 (34.2)	8 (11.9)	**0.002**	17 (26.6)	18 (22.0)	0.561
- Alive at discharge	111 (76.0)	52 (65.8)	59 (88.1)		47 (73.4)	64 (78.0)	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, NICU: neonatal intensive care unit.

Table 5. Outcome of live born AGA and SGA infants between cohort I and II.

	AGA Cohort I n=38	AGA Cohort II n=43	Cohort I vs II
Outcome AGA			p-value
Died in delivery room	3 (7.9)	14 (32.6)	**0.012**
Admitted to NICU	35 (92.1)	29 (67.4)	
- Died in NICU	10 (28.6)	7 (21.4)	0.780
- Alive at discharge	25 (71.4)	22 (75.9)	
	SGA Cohort I n=56	**SGA Cohort II** n=42	**Cohort I vs II**
Outcome SGA			p-value
Died in delivery room	12 (21.4)	4 (9.5)	0.168
Admitted to NICU	44 (78.6)	38 (90.5)	
- Died in NICU	17 (38.6)	1 (2.6)	**<0.001**
- Alive at discharge	27 (61.4)	37 (97.4)	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, NICU: neonatal intensive care unit.

Discussion

Survival and Neonatal Morbidity

The survival rate of our study population of live-born infants with a BW of ≤750 g was 62%. Mortality can be summarized as follows: one third died before delivery, mainly due to placental insufficiency; one fifth died in the delivery room because active resuscitation was withheld or discontinued in view of extreme prematurity, and one fifth died during NICU stay, of which the majority died within the first week of life mainly due to severe cardiorespiratory failure.

The main reason for the relatively high percentage of antenatal deaths due to termination of pregnancy for maternal reasons (due to deteriorating preeclampsia, eclampsia or HELLP syndrome) is the level three function of Wilhelmina Children's Hospital, which results in a high prevalence of seriously ill women who are referred by regional hospitals (unpublished data). Wilson-Costello et al.[1] reported immaturity to be the main cause of death in 46% of the infants with a BW of 500–749 g (born between 1990 and 1998), and 35% of these infants died due to respiratory distress and sequelae. Hack et al.[6] also found immaturity (55%) to be the main cause of death and 22% died due to respiratory distress syndrome (infants with a BW of 500–750 g born in 1990–1992). Fanaroff et al.[22] found respiratory distress syndrome and early onset septicemia to be important risk factors for mortality.

Other studies reported varying survival rates for infants with a BW of ≤750 g. Survival rates of these ELBW infants born between 1990 and 2005 ranged from 37.7 to 55%.[7,12,22,23] All survival rates cited were lower than ours, except for Itabashi et al.[24] who reported a survival rate of 75.2% for infants with a BW of <800 g born in 2005.
Poor survival of ELBW infants is strongly related to GA at birth. Tommiska et al.[12] showed a survival rate of 47–73% for infants born between 1999 and 2000 at 24 and 26 weeks of gestation, respectively. Moro et al.[7] also showed an increase in survival rate in infants born between 2002 and 2005 ranging from 58.4% for 25–26 weeks of gestation to 95.5% for a GA of >30 weeks. Itabashi et al.[24] reported a survival rate of 76.6% for infants born in 2005 at 24 weeks of gestation and a 91.7% survival rate for infants of ≥28 weeks of gestation. The EXPRESS group[25] found a survival rate of 67% for infants born at 24 weeks of gestation between 2004 and 2007 and 85% for infants born at 26 weeks of gestation.
Differences found in the survival rates may be partly due to differences in inclusion criteria regarding the lower limit of gestation and different policies regarding resuscitation in the delivery room and/or allowing antenatal death to occur without active intervention.
Several studies have shown that a multiple pregnancy is a high risk situation resulting in a significantly higher prevalence of morbidity and poor survival.[26,28] 22.8% of our infants were part of a multiple pregnancy, which may have influenced outcome.
Unlike other reports showing a better outcome for female infants, our study did not show a difference in survival and neonatal morbidity between male and female infants, despite a significantly lower mean BW of female infants (641 vs. 673 g, p = 0.008) and similar GA of 28 weeks.[29,30]
The infants who were admitted to the NICU experienced considerable neonatal morbidity. The majority of the infants needed long-term NICU admission and required mechanical ventilation due to respiratory problems caused by IRDS and its complications. Also a great number of infants received inotropes for hypotension. About one third was diagnosed with PVL grade I and one fourth with IVH grade I/II, but severe intracranial lesions were not common. Other studies on neonatal morbidity in ELBW infants show similar results and confirm the vulnerability of these infants. In infants with a BW of ≤750 g born between 1990 and 2002, IRDS was found in 64–71%, BPD in 41–46%, septicemia in 12–53%, NEC in 4–14%, IVH grade I/II in 19–28.6%, and IVH grade III/IV in 12–24%.[6,22,23]

Outcome of Cohort I Compared to Cohort II

Survival of infants with a BW of ≤750 g, admitted to the NICU, significantly improved over the two time periods studied.
We found no significant difference in the number of cesarean sections between the two cohorts, therefore the outcome of the infants in both cohorts did not appear to be affected by changes in obstetrical care. The infants of cohort II had a significantly

higher mean BW, and this may partly explain the improved survival. Several studies confirmed that survival is positively related to a higher BW.[12,22,24]

The infants of cohort II experienced respiratory problems significantly less often, resulting in significantly fewer infants who needed mechanical ventilation. Since 1999, the children's hospital moved from within the center of Utrecht to the site where the obstetric unit was located. As transfer across two hospitals was no longer required, more infants were started and could be maintained on continuous positive airway pressure. Significantly more infants in cohort I required mechanical ventilation for more than 4 weeks, most likely due to a significantly higher prevalence of IRDS grade III/IV. Multivariate regression analysis confirmed IRDS grade III/IV and long-term ventilation to be predictive for survival outcome (p = 0.003). The need for prolonged ventilation is known to be a poor prognostic factor for survival and neurodevelopmental outcome, due to a high risk of pressure-related pulmonary damage and cerebral hemorrhages.[17,31]Another possible explanation for the higher survival rate of cohort II infants could possibly be the more aggressive measures in obstetrical care, resuscitation and support of extremely preterm and low BW infants. Changes in perinatal care, such as administration of antenatal steroids, and advances in postnatal care including use of surfactant and high frequency oscillatory ventilation, led to improved survival of ELBW infants.[1-6] However, our study did not find changes in the administration of antenatal steroids and surfactant between the two time periods studied.

The increased survival resulted from significantly fewer infants who died after withdrawal of intensive care due to severe cardiorespiratory failure or severe cerebral lesions in cohort II. This could be partly explained by the poorer condition (higher prevalence of BPD, IRDS grade III/IV and mechanical ventilation >4 weeks) of infants in cohort I. Probably small improvements in neonatal treatment and differential application of the withdrawal criteria in cohort II may have accounted for this as well.

The higher prevalence of septicemia in cohort II may be explained by a longer stay in the NICU as significantly more infants who had been admitted for more than 28 days developed septicemia, although the number of infants who were admitted for more than 28 days did not differ between cohort I and II. Furthermore the increased rate of septicemia may also have resulted from the gradually increased prevalence of invasive procedures as umbilical lines in cohort II.

An explanation for the higher prevalence of hyperbilirubinemia in cohort II could be associated with the increased rate of septicemia with concomitant hemolysis.[27]

Other studies also demonstrated increased survival for ELBW infants, nevertheless varying survival rates are found, but merely being consistent with our improved survival rates. Hack et al.[6] reported an increase in survival from 24 to 43% (p < 0.005) in infants with a BW of <750 g (1982–1988 compared to 1990–1992). Wilson-Costello et al.[1] showed significantly improved survival rates from 27 to 48% (p <

0.001) in infants with a BW of 500–749 g (1982–1989 compared to 1990–1998). Doyle et al.[32] reported a significant increase in survival from 32 to 61.1% ($p < 0.001$) in infants with a BW of 500–749 g born in 1991–1992 compared to 1997. The studies cited are in agreement with our significantly improved survival rates over time for infants with a BW of ≤750 g.

Tommiska et al.[12] however found no significant improvement in survival for infants with a BW of 500–749 g (survival rate 45% in 1996–1997 to 52% in 1999–2000). Still comparing these studies with our data is complicated due to differences in inclusion criteria regarding the lower limit of gestation. Furthermore it is often not clearly stated whether antenatal death was accepted in infants with a very poor prognosis or whether some infants were not resuscitated in the delivery room for the same reason. These differences in policy make it difficult to compare our survival data with other studies.

Criteria to initiate intensive care in infants with a GA of <26 weeks is changing in the Netherlands, but during the study period intensive care was generally not offered to infants with a GA of 24 weeks or born at 25 weeks but presenting with perinatal asphyxia or severe respiratory problems at delivery. From 2007 onwards, there has been a gradual change in attitude in our hospital to be more active in the delivery room and also to intubate infants born at 25 weeks of gestation who show severe signs of respiratory failure immediately after birth.

SGA and AGA Infants

In our study population survival of SGA and AGA infants was similar, however survival of SGA infants increased significantly with time. Significantly more SGA infants were delivered by cesarean section. For both groups fetal distress was the main reason for performing a cesarean section.

The AGA infants of our study population were born at a significantly lower mean GA. Due to the fact that AGA infants were born significantly more prematurely, we would have expected to find a greater survival advantage for SGA infants. Other studies support that better survival is positively related to the length of gestation.[2,3,23,31]

The majority of the SGA infants were of male gender, and from other studies it is known that female neonates have a better chance of survival compared to their male peers.[28-30] Interestingly male gender did not affect the survival of our SGA infants in a negative way.

During NICU stay, AGA infants required mechanical ventilation significantly more often. This was due to a higher prevalence of IRDS in AGA infants and their significantly shorter GA may have accounted for this as well.

PDA was diagnosed significantly more often in AGA infants. The literature has shown that infants with PDA may be at increased risk of NEC, BPD, or IVH, and the negative effects of PDA treatment on neurodevelopmental outcome have also been reported. Madan et al.[33] showed that infants treated with surgery for PDA may

be at increased risk of poor short- and long-term outcomes compared with those treated with indomethacin. However, in our study population the majority of infants diagnosed with a PDA was treated with indomethacin.

The SGA infants as well as the AGA infants included in our study population were ELBW infants. These infants are known to be prone to severe neonatal morbidity.[6-8] In addition Regev et al.[10] showed that SGA infants are at increased risk of BPD and retinopathy of prematurity. Bernstein et al.[11] showed a significant association of IUGR with NEC, IRDS and a trend toward association of IUGR with an increased risk of IVH. These results are not in agreement with the higher prevalence of severe neonatal morbidity found in AGA infants compared to the SGA infants of our cohort. However, the above-mentioned significantly shorter GA of AGA infants most likely resulted in more severe neonatal morbidity in these infants compared to SGA infants. We are of the opinion that the ELBW-based inclusion may possibly have influenced the outcome results. Despite significantly more severe neonatal morbidity in AGA infants, no negative effect was noticed on their survival.

When comparing the outcome of SGA and AGA infants between cohorts I and II, survival of SGA was noted to increase with time whereas survival of AGA infants remained unchanged. Other reports on mortality merely show disappointing outcomes for SGA infants compared to AGA infants. Kono et al.[9] showed a 2.4-fold increased risk of mortality in SGA infants. Regev et al.[10] even showed a 4.5-fold higher risk of death in SGA infants. Bernstein et al.[11] showed a statistically significant association between IUGR and neonatal death (odds ratio 2.77). Whereas Kono et al.[9] showed a nonsignificant survival advantage for AGA infants (84.0 vs. 72.1% in SGA infants), no significant change in survival rate was noted over time in either the SGA or AGA group. Our similar survival rates of SGA and AGA infants and the increasing survival rate of both SGA and AGA infants are not in agreement with the findings of these studies. However comparing our results of SGA and AGA infants with other studies remains difficult due to differences in definition of SGA and varying obstetrical and perinatal policies as discussed above. Nevertheless our survival rates for SGA and AGA infants show promising results with increased survival for both SGA and AGA infants. Despite this increase in survival, these infants are known to be at risk of a poor long-term outcome. They should therefore be followed carefully because they are prone to cognitive and motor problems in later life.[1-3,6,12,13] The 2-year outcome data of the survivors of our study population will be reported separately.[34]

A limitation of this study is its retrospective design, and the relatively small number of infants born in a single level three unit. However we have presented a cohort study of infants born during a 10-year time period.

Conclusion

The mortality of infants with a BW of ≤750 g is high, but decreases with time, especially for SGA infants. However, considerable neonatal morbidity was present, especially in AGA infants, most likely due to their significantly shorter GA.
Medical decision making and counseling should be based on an estimation of the individual prognosis for these children. Further research in a larger study population, regarding short-term survival as well as development into childhood and adolescence, is required as these infants often grow into their deficits.

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Two-year neurodevelopmental outcome of preterm born children ≤ 750g at birth

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Abstract

Objectives To describe 2-year neurodevelopmental outcome (NDO) in a cohort of extremely low birth weight infants, and compare NDO between two consecutive 5-year periods and between appropriate (AGA, ≥p10) and small for gestational age (SGA, <p10) children.

Design Retrospective cohort study.

Setting Wilhelmina Children's Hospital, Utrecht, the Netherlands.

Patients 146 children, born between 1996 and 2005, with a birth weight ≤750g and a gestational age ≥24 weeks, admitted to the neonatal intensive care unit. 111 children (76%) survived the neonatal period.

Interventions At 2 years corrected age 101 children (cohort I: born in 1996-2000, n=45 and cohort II: born in 2001-2005, n=56) were assessed with either the Griffiths Mental Developmental Scales or the Mental Scale of the Bayley Scales of Infant Development-second edition.

Main outcome measures NDO, classified as normal: (Z-score ≥-1), mildly delayed (-2 ≤ Z-score < -1) or severely delayed (Z-score < -2).

Results 74.3% of the children had a normal NDO at 2 years corrected age, 20.8% a mildly and 5% a severely delayed outcome. Although survival significantly increased with time (65.8% to 88.1%, p=0.002), significantly fewer children in cohort II (66.1% vs 84.4% in cohort I, p=0.042) as well as fewer SGA children (64.3% vs 86.7% of AGA children, p=0.012) had a normal NDO.

Conclusions Increased survival of infants with a birth weight ≤750g coincided with more children with an impaired NDO at 2 years corrected age. SGA children are especially at risk of impaired NDO.

Introduction

Changes in perinatal and neonatal care, such as increased use of prenatal steroids, early assisted ventilation in the delivery room and advanced techniques for mechanical ventilation in combination with surfactant therapy, have resulted in improved survival rates for extremely preterm and extremely low birth weight (ELBW) infants.[1-10] Although it is promising that survival of ELBW infants has improved, it is well known that survivors are at increased risk of impaired neurodevelopmental outcome (NDO).[2, 3, 11-15] Studies on the NDO of ELBW children show contradictory results, with varying prevalence of cognitive impairment between 10.6% and 50%, which either increased, decreased or remained unchanged over time.[1-3, 13-18]
The objectives of this retrospective cohort study of children with a birth weight ≤750g were to assess NDO at 2 years corrected age, and to compare NDO between two consecutive 5-year periods of birth and between children who were either appropriate (AGA) or small for gestational age (SGA).

Methods

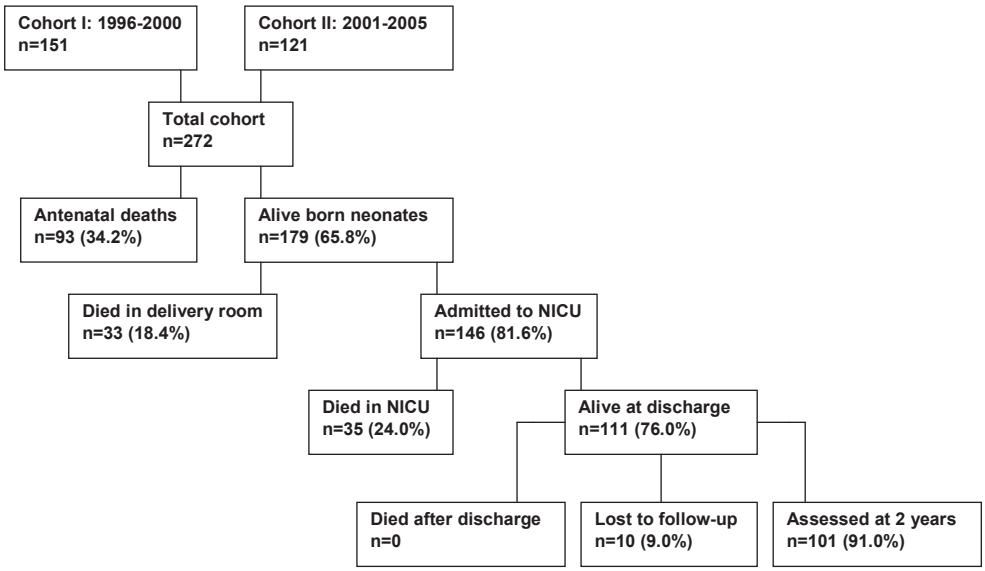
Subjects

The study population consisted of a cohort of 272 infants with a birth weight ≤750g and a gestational age ≥24 completed weeks, born in 1996 through to 2000 (cohort I) and 2001 through to 2005 (cohort II). Ninety-three (34.2%) infants were intrauterine deaths and 179 (65.8%) were live born infants. A total of 146 infants were admitted to the neonatal intensive care unit (NICU) of the Wilhelmina Children's Hospital in Utrecht in the Netherlands (130 infants (89%) were born in our university hospital, the remaining 16 infants were transported to our NICU after delivery in a regional hospital). Of the 111 survivors, 91% (cohort I, n=45 and cohort II, n=56) were available for follow-up at 2 years corrected age (Figure 1).

Data collection and definitions

Data were collected by reviewing the medical charts. Gestational age was based on the last menstrual period and early ultrasound examination. Birth weight percentiles were determined according to the Netherlands Perinatal Registry.[19] SGA was defined as a birth weight less than the 10th percentile (p10). NICU admission was divided into short-term (≤28 days) or long-term (>28 days) stay. Mechanical ventilation was recorded as short-term (<2 weeks), intermediate (2-4 weeks) or long-term (>4 weeks). Oxygen requirement was recorded. Infant respiratory distress syndrome (IRDS) grades I-IV were defined according to Giedion.[20] Bronchopulmonary dysplasia (BPD) was defined as the need for oxygen at 36 weeks post menstrual age according to Northway.[21] Antenatal bethametasone and postnatal hydrocortisone use were registered. Hypotension was defined according to postnatal age specific blood pressure standards and treatment with inotropes was registered. Persistent ductus arteriosus (PDA) was diagnosed clinically and confirmed by cardiac ultrasound.

Figure 1. Cohort of 272 infants with a birth weight ≤ 750g born in 1996-2005.



Treatment of PDA with indomethacin or surgery was recorded. Periventricular leukomalacia (PVL) and intraventricular haemorrhage (IVH) were graded according to de Vries et al.[22] Septicaemia was defined as clinical signs in combination with a positive blood culture. Necrotizing enterocolitis (NEC) was classified according to Bell.[23] Surgical treatment of NEC was recorded. Hyperbilirubinaemia was registered as needing phototherapy according to postnatal age specific bilirubin levels.[24] Hypothyroidism was diagnosed according to postnatal age specific standards for free T4 and TSH.[25] Hypoglycaemia and hyperglycaemia were defined as a plasma glucose of <2.6mmol/l and >8.0mmol/l, respectively.[26] Retinopathy of prematurity (ROP) was classified according to the international classification.[27,28] Parental educational levels were recorded according to the occupational classification standard of Statistics Netherlands.[29] Socio-economic status (SES) was recorded according to the zip code estimated income of The Netherlands Institute for Social Research.[30]

Neurodevelopmental assessments

For our primary outcome, data on NDO at or near 2 years corrected age were collected. NDO was evaluated using either the Griffiths Mental Developmental Scales (GMDS) or the Bayley Scales of Infant Development-second edition (BSID-II), administered by certified investigators. Both tests are most reliable when performed at or around 24 months corrected age. The GMDS consists of five subscales: locomotion, personal-social, hearing-speech, eye-hand, and performance. This test is designed to yield both global (sum of five subscales) and subscale developmental quotients (DQ) with

a mean (±SD) DQ score for the general population of 100 (±12).[31] Assessment of neurodevelopment with the GMDS in our study is based on four subscales, excluding locomotion.[32]

The BSID-II consists of a Mental Scale and a Psychomotor Scale, for neurodevelopmental assessment the mental developmental index (MDI) was used, with a mean of 100 (±15).[33] In case of a MDI <55, 54 was entered in the dataset.

For calculation of developmental scores the accurate gestational age in fractions (such as 25 weeks and 1/7 week) was used. These fractions were transformed into decimals by SPSS (resulting in 1 day = 0.14 week, etc). Developmental scores were calculated both for chronological age and corrected age. A correction for prematurity was made by subtracting the amount of prematurity (40 minus gestational age at birth) from the actual age at testing.

From December 2000 onward, all but six children were assessed with the BSID-II due to recent implementation of guidelines of the Dutch National follow-up working group. Z-scores were calculated for both GMDS (DQ without locomotion subscale) and BSID-II (MDI) outcomes in order to compare these neurodevelopmental scores. NDO was classified as normal: (Z-score ≥-1), mildly delayed (-2 ≤ Z-score < -1) or severely delayed (Z-score < -2).

Statistical analysis

To check for accuracy, data entered were double checked. All analyses were performed using SPSS version 15.0. Statistical comparisons for continuous variables were made with Mann-Whitney tests. Dichotomous and categorical variables were tested using the Chi-square test or Fisher's exact test. Univariate and multivariate analyses for continuous variables were performed by linear regression, and for dichotomous variables logistic regression was used. A p value <0.05 was considered to be statistically significant.

Results

Figure 1 shows a flow chart of the initial study population (n=272). The survival rate of all NICU admissions (n=146) was 76% and increased with time from 65.8% (52/79) in cohort I to 88.1% (59/67) in cohort II (p=0.002). No significant difference in survival was noted between AGA and SGA infants (73.4% (47/64) and 78% (64/82), p=0.561). However, the survival of SGA infants significantly increased with time (61.4% (27/44) to 97.4% (37/38), p<0.001), whereas the survival of AGA infants remained unchanged (71.4% (25/35) to 75.9% (22/29), p=0.780).[6] In 101/111 (91%) of the surviving children, NDO was assessed at 2 years corrected age.

Table 1 shows the most relevant characteristics of these 101 infants. A significantly higher birth weight was noted in cohort II (685g vs 649g, p=0.025). The median gestational age of both cohorts I and II was 28 weeks. As expected, SGA infants

Table 1. Characteristics of 101 surviving children assessed at 2 years corrected age: total cohort, cohort I and II, and AGA and SGA infants.

	Total cohort	By cohort			By gestational age		
		Cohort I	Cohort II	Cohort I vs II	AGA	SGA	AGA vs SGA
	n=101	n=45	n=56		n=45	n=56	
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Median maternal age (years) (min-max)	30.0 (17-45)	29.0 (19-43)	31.0 (17-45)	0.198	29.0 (19-43)	31.0 (17-45)	0.173
Median birth weight (gram) (min-max)	675 (480-750)	649 (480-750)	685 (540-750)	**0.025**	720 (580-750)	635 (480-750)	**<0.001**
Median gestational age (weeks) (min-max)	28.00 (24.84-34.42)	27.84 (24.84-34.42)	28.21 (25.0-34.14)	0.205	26.70 (24.84-29.42)	28.84 (26.28-34.42)	**<0.001**
Multiple birth	20 (19.8)	8 (17.8)	12 (21.4)	0.803	13 (28.9)	7 (12.5)	**0.048**
Male	45 (44.6)	20 (44.4)	25 (44.6)	1.000	15 (33.3)	30 (53.6)	**0.047**
Ethnicity (Caucasian)	93 (92.1)	43 (95.6)	50 (89.3)	0.293	40 (88.9)	53 (94.6)	0.461
SES				0.515			0.429
-High	21 (21.0)	7 (15.6)	14 (25.5)		9 (20.5)	6 (10.7)	
-Average	64 (64.0)	31 (68.9)	33 (60.0)		26 (59.1)	38 (67.9)	
-Low	15 (15.0)	7 (15.6)	8 (14.5)		9 (20.5)	12 (21.4)	
Maternal educational level				**0.019**			0.308
-High	12 (17.9)	1 (3.3)	11 (29.7)		5 (15.6)	7 (20.0)	
-Average	28 (41.8)	14 (46.7)	14 (37.8)		11 (34.4)	17 (48.6)	
-Low	27 (40.3)	15 (50.0)	12 (32.4)		16 (50.0)	11 (31.4)	
Prenatal steroids (GA <32 weeks)	81 (86.2)	34 (82.9)	47 (88.7)	0.549	39 (86.7)	42 (85.7)	1.000
Caesarean delivery	83 (82.2)	36 (80.0)	47 (83.9)	0.794	27 (60.0)	56 (100)	**<0.001**
5–min Apgar score <7	12 (11.9)	6 (13.3)	6 (10.7)	0.762	8 (17.8)	4 (7.1)	0.127
SGA	56 (55.4)	22 (48.9)	34 (60.7)	0.314	-	-	-

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, GA: gestational age, SGA: small for gestational age <p10. AGA: appropriate for gestational age ≥p10, SES: socio-economic status, Maternal educational level was available in 87.1%.

had a significantly lower birth weight than AGA infants (635 vs 720g, $p<0.001$), whereas a significantly shorter gestational age was found in AGA infants (26.70 vs 28.84 weeks, $p<0.001$). Maternal education was significantly lower in cohort I ($p=0.019$). All SGA infants were delivered by caesarean section compared to 60% of the AGA infants ($p<0.001$).

Neonatal morbidity during NICU admission

The majority of the infants required NICU admission for at least 4 weeks (Table 2). One in five infants did not need mechanical ventilation. IRDS grade I/II and III/IV were both diagnosed in almost 30% and the majority of the infants with IRDS received surfactant. BPD developed in 56.4%, and over 70% of the BPD cases received hydrocortisone treatment. In 62.4% hypotension was present and the majority needed treatment with inotropes. PDA was diagnosed in one third, almost 56% received indomethacin and about 15% required surgical closure. Cranial ultrasound showed PVL grade I in 43.6%, IVH grade I/II in 20%

and severe intracranial lesions (IVH grade III/IV or cystic-PVL grade II) were found in 5%. None of them developed cystic-PVL grade III. Septicaemia occurred in 61.4%. NEC was diagnosed in 8.9%, the majority required a laparotomy. Furthermore, a high prevalence of hyperbilirubinaemia was noted. ROP (any stage) developed in 46.5%, but more severe ROP (stage III, IV and V) was present in only 5% of the children, none of these required laser surgery (though, one child received a cerclage because of retinal detachment).

In cohort I a significantly higher prevalence of IRDS grade III/IV ($p=0.042$), BPD ($p=0.002$) and mechanical ventilation >4 weeks ($p=0.008$) was present, whereas significantly more hyperbilirubinaemia was found in cohort II ($p=0.022$).

A significantly higher prevalence of IRDS ($p=0.033$), mechanical ventilation >4 weeks ($p=0.002$) and PDA ($p=0.019$) was noted in AGA infants, as well as treatment with indomethacin ($p=0.038$).

Neurodevelopmental outcome at 2 years corrected age

Overall, 101 children were assessed by either the GMDS (n=49) or the BSID-II (n=52). The mean age at testing was 23.4 months (SD 1.8 months) corrected age.

In Table 3 the mean neurodevelopmental scores and Z-scores are presented. No significant differences were noted between the corrected Z-scores of the GMDS and BSID-II ($p=0.661$). (For completeness uncorrected scores are shown in the tables as well). The total cohort performed within 1 SD below the population mean (Z-score -0.37). The scores between cohort I and II were not significantly different ($p=0.164$), but SGA children scored almost significantly lower compared to AGA children (-0.54 vs -0.15, $p=0.050$).

Table 2. Neonatal morbidity and interventions during NICU admission.

	Total cohort	By cohort			By gestational age		
		Cohort I	Cohort II	Cohort I vs II	AGA	SGA	AGA vs SGA
	n=101	n=45	n=56		n=45	n=56	
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
NICU admission >28 days	87 (86.1)	39 (86.7)	48 (85.7)	0.890	38 (84.4)	49 (87.5)	0.774
Ventilation				**0.021**			**0.002**
- no	20 (19.8)	5 (11.1)	15 (26.8)		5 (11.1)	15 (26.8)	
- short <2 weeks	29 (28.7)	11 (24.4)	18 (32.1)		9 (20.0)	20 (35.7)	
- intermediate 2-4 weeks	36 (35.6)	17 (37.8)	19 (33.9)		18 (40.0)	18 (32.1)	
- long >4 weeks	16 (15.8)	12 (26.7)	4 (7.1)		13 (28.9)	3 (5.4)	
Oxygen >21%	92 (91.1)	44 (97.8)	48 (85.7)	**0.040**	41 (91.1)	51 (91.1)	1.000
IRDS				0.126			**0.033**
-no	43 (42.6)	16 (35.6)	27 (48.2)		13 (28.9)	30 (53.6)	
-grade I/II	28 (27.7)	11 (24.4)	17 (30.4)		24 (31.1)	14 (25.0)	
-grade III/IV	30 (29.7)	18 (40.0)	12 (21.4)		18 (40.0)	12 (21.4)	
Surfactant for IRDS	43 (74.1)	21 (72.4)	22 (75.9)	0.764	25 (78.1)	18 (69.2)	0.550
BPD	57 (56.4)	33 (73.3)	24 (42.9)	**0.002**	29 (64.4)	28 (50.0)	0.163
- hydrocortisone for BPD	37 (64.9)[a]	22 (66.7)	15 (62.5)	0.745	18 (62.1)	19 (67.9)	0.783
- hydrocortisone for BPD and hypotension	7 (17.5)[b]	6 (27.3)	1(5.6)	0.105	6 (28.6)	1 (5.3)	0.095
Hypotension	63 (62.4)	30 (66.7)	33 (58.9)	0.425	30 (66.7)	33 (58.9)	0.536
Treatment for hypotension				0.347			0.898
- inotropes	49 (77.8)[c]	24 (80.0)	25 (75.8)		23 (76.7)	26 (78.8)	
- iv fluids only	11 (17.5)[c]	6 (20.0)	5 (15.2)		6 (20.0)	5 (15.2)	

	Total cohort	By cohort			By gestational age		
		Cohort I	Cohort II	Cohort I vs II	AGA	SGA	AGA vs SGA
	n=101	n=45	n=56		n=45	n=56	
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Treatment for PDA				0.204			**0.038**
- spontaneous closure	10 (29.4)[d]	7 (41.2)	3 (17.6)		5 (23.8)	5 (38.5)	
- indomethacin	19 (55.9)[d]	9 (52.9)	10 (58.8)		15 (71.4)	4 (30.8)	
- surgery	5 (14.7)[d]	1 (5.9)	4 (23.5)		1 (4.8)	4 (30.8)	
PVL				0.748			0.539
- no	56 (55.4)	25 (55.6)	31 (55.4)		26 (57.8)	30 (53.6)	
- grade I	44 (43.6)	19 (42.2)	25 (44.6)		18 (40.0)	26 (46.4)	
- grade II	1 (1.0)	1 (2.2)	0		1 (2.2)	0	
IVH				0.690			0.270
- no	75 (74.3)	33 (73.3)	42 (75.0)		31 (68.9)	44 (78.6)	
- grade I/II	22 (21.8)	11 (24.4)	11 (19.6)		13 (28.9)	9 (16.1)	
- grade III/IV	4 (4.0)	1 (2.2)	3 (5.4)		1 (2.2)	3 (5.4)	
Septicaemia	62 (61.4)	26 (57.8)	36 (64.3)	0.504	26 (57.8)	36 (64.3)	0.542
NEC	9 (8.9)	2 (4.4)	7 (12.5)	0.292	4 (8.9)	5 (8.9)	1.000
- surgery for NEC	8 (88.9)[e]	2 (100)	6 (85.7)	1.000	3 (75.0)	5 (100)	0.444
Hyperbilirubinemia	80 (79.2)	31 (68.9)	49 (87.5)	**0.022**	36 (80.0)	44 (78.6)	1.000
Hypoglycaemia	24 (23.8)	9 (20.0)	15 (26.8)	0.426	9 (20.0)	15 (26.8)	0.486
Hyperglycaemia	29 (28.7)	10 (22.2)	19 (33.9)	0.196	15 (33.3)	14 (25.0)	0.384
Hypothyroidism	4 (4.0)	4 (8.9)	0	**0.036**	1 (2.2)	3 (5.4)	0.627

	Total cohort	By cohort			By gestational age		
		Cohort I	Cohort II	Cohort I vs II	AGA	SGA	AGA vs SGA
	n=101	n=45	n=56		n=45	n=56	
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
ROP				0.780			0.873
- stage I	35 (34.7)	14 (31.1)	21 (37.5)		16 (35.6)	19 (33.9)	
- stage II	7 (6.9)	4 (8.9)	3 (5.4)		3 (6.7)	4 (7.1)	
- stage III	4 (4.0)	2 (4.4)	2 (3.6)		1 (2.2)	3 (5.4)	
- stage IV	1 (1.0)	1 (2.2)	0		1 (2.2)	0	
- stage V	0	0	0		0	0	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10. NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PDA: patent ductus arteriosus, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis. a: % of patients who suffered BPD, b: % of patients who suffered BPD and hypotension, c: % of patients who suffered hypotension, d: % of patients who suffered PDA, e: % of patients who suffered NEC. ROP: retinopathy of prematurity. Comparisons were made based on a Chi-square test or Fisher's exact test where appropriate.

Table 3. Neurodevelopmental outcome at 2 years corrected age of 101 children birth weight ≤ 750g.

	By developmental test			Total cohort*	By cohort			By gestational age		
	GMDS n=49	BSID n=52	GMDS vs BSID	n=101	Cohort I* n=45	Cohort II* n=56	Cohort I vs II	AGA* n=45	SGA* n=56	AGA vs SGA
	(SD, min~max)	(SD, min~max)	p-value	(SD, min~max)	(SD, min~max)	(SD, min~max)	p-value	(SD, min~max)	(SD, min~max)	p-value
Corrected absolute score	96.45 (9.8, 80~127)	93.50 (18.4, 54~128)	-	94.93 (14.8, 54~128)	97.63 (9.8, 80~127)	92.76 (17.7, 54~128)	-	97.97 (14.1, 54~127)	92.49 (15.1, 58~128)	-
Z-score corrected	-0.30 (0.8, -1.69~2.23)	-0.43 (1.2, -3.07~1.87)	0.661	-0.37 (1.0, -3.07~2.23)	-0.20 (0.8, -1.69~2.23)	-0.50 (1.2, -3.07~1.87)	0.164	-0.15 (1.0, -3.07~2.23)	-0.54 (1.0, -2.80~1.87)	0.050
Uncorrected absolute score	86.08 (8.4, 72~113)	83.85 (15.6, 54~114)	-	84.93 (12.6, 54~114)	86.90 (8.4, 72~113)	83.35 (15.0, 54~114)	-	86.56 (12.0, 54~113)	83.62 (13.0, 54~114)	-
Z-score uncorrected	-1.16 (0.7, -2.36~1.11)	-1.08 (1.0, -3.07~0.93)	0.599	-1.12 (0.9, -3.07~1.11)	-1.08 (0.7, -2.36~1.11)	-1.15 (1.0, -3.07~0.93)	0.599	-1.00 (0.9, -3.07~1.11)	-1.20 (0.9, -3.07~0.93)	0.228

GMDS: Griffiths Mental Development Scales, Developmental Quotient, locomotor subscale excluded, GMDS Standardization mean (±SD)= 100(±12) BSID-II: Bayley Scales of Infant Development-Second Edition, Mental Developmental Index (MDI), BSID-II standardization mean (±SD)= 100 (±15), Cohort I: 1996-2000, Cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10. *GMDS DQ-LM and BSID-II MDI combined. SD: standard deviation, min: minimum raw score, max: maximum raw score.

Table 4. Neurodevelopmental outcome of total cohort, cohorts I and II, and AGA and SGA infants.

	Total cohort	By cohort			By gestational age		
	n=101	Cohort I n=45	Cohort II n=56	Cohort I vs II p-value	AGA n=45	SGA n=56	AGA vs SGA p-value
Outcome CA							
Normal, n (%)	75 (74.3)	38 (84.4)	37 (66.1)	0.051	39 (86.7)	36 (64.3)	**0.020***
Mildly delayed, n (%)	21 (20.8)	7 (15.6)	14 (25.0)		4 (8.9)	17 (30.4)	
Severely delayed, n (%)	5 (5.0)	0	5 (8.9)		2 (4.4)	3 (5.4)	
Outcome UCA							
Normal, n (%)	43 (42.6)	18 (40.0)	25 (44.6)	0.079	21 (46.7)	22 (39.3)	0.359
Mildly delayed, n (%)	41 (40.6)	23 (51.1)	18 (32.1)		19 (42.2)	22 (39.2)	
Severely delayed, n (%)	17 (16.8)	4 (8.9)	13 (23.2)		5 (11.1)	12 (21.4)	

UCA: uncorrected age, CA: corrected age for prematurity, total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥p10, SGA: small for gestational age <p10, Outcome: Griffiths Mental Development Scales, Developmental Quotient, locomotor subscale excluded and Bayley Scales of Infant Development-Second Edition, Mental Developmental Index, Normal: Z-score ≥ -1, performance within -1 SD or > 0 SD, Mildly delayed: -2 ≤ Z-score < -1, performance within -1 and -2 SD, Severely delayed: Z-score < -2, performance more than -2 SD. * indicates $p < 0.05$.

Table 4 shows a classification of Z-scores into three categories: 74.3% of the children had a normal NDO, 20.8% a mildly delayed and 5% a severely delayed outcome. Significantly more children in cohort I performed within normal limits (84.4% vs 66.1%, p=0.042), fewer had a mildly delayed (15.6% vs 25%) and none had a severely delayed performance compared to 8.9% in cohort II.

The difference in NDO between cohort I and II slightly attenuated after adjustment for potential confounding by the variables ventilation >4 weeks, IRDS grade III/IV, BPD, hydrocortisone, oxygen and hyperbilirubinaemia (p=0.040 for linear analysis, p=0.123 for logistic analysis, p=0.055 using propensity score).

A significantly poorer outcome was found in SGA children (p=0.020). Significantly fewer SGA children performed within normal limits (64.3% vs 86.7%, p=0.012).

No significant difference in NDO was found between AGA children in cohort I and cohort II, neither between SGA children in cohort I and II (p=0.906 and p=0.129 respectively, Table 5).

Table 5. Neurodevelopmental outcome of AGA and SGA infants between the two cohorts.

	AGA Total cohort n=45	AGA Cohort I n=23	AGA Cohort II n=22	Cohort I vs II p-value
Corrected age				
Mean (SD, min-max)	-0.15 (1.0, -3.07~2.23)	-0.07 (0.9, -1.64~2.23)	-0.22 (1.1, -3.07~1.67)	0.906
Normal, n (%)	39 (86.7)	21 (91.3)	18 (81.8)	0.444
Mildly delayed, n (%)	4 (8.9)	2 (8.7)	2 (9.1)	
Severely delayed, n (%)	2 (4.4)	0	2 (9.1)	
Uncorrected age				
Mean (SD, min-max)	-1.00 (0.9, -3.07~1.11)	-1.04 (0.8, -2.36~1.11)	-0.97 (1.0, -3.07~0.60)	0.593
Normal, n (%)	21 (46.7)	9 (39.1)	12 (54.5)	0.447
Mildly delayed, n (%)	19 (42.2)	12 (52.2)	7 (31.8)	
Severely delayed, n (%)	5 (11.1)	2 (8.7)	3 (13.6)	
	SGA Total cohort n=56	**SGA Cohort I n=22**	**SGA Cohort II n=34**	**Cohort I vs II p-value**
Corrected age				
Mean (SD, min-max)	-0.54 (1.0, -2.80~1.87)	-0.32 (0.7, -1.69~0.86)	-0.69 (1.2, -2.80~1.87)	0.129
Normal, n (%)	36 (64.3)	17 (77.3)	19 (55.9)	0.205
Mildly delayed, n (%)	17 (30.4)	5 (22.7)	12 (35.3)	
Severely delayed, n (%)	3 (5.4)	0	3 (8.8)	
Uncorrected age				
Mean (SD, min-max)	-1.20 (0.9, -3.07~0.93)	-1.12 (0.6, -2.26~-0.02)	-1.26 (1.0, -3.07~0.93)	0.353
Normal, n (%)	22 (39.3)	9 (40.9)	13 (38.2)	0.202
Mildly delayed, n (%)	22 (39.2)	11 (50.0)	11 (32.4)	
Severely delayed, n (%)	12 (21.4)	2 (9.1)	10 (29.4)	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age ≥ p10, SGA: small for gestational age < p10, Normal: Z-score ≥ -1, performance within -1 SD or > 0 SD, Mildly delayed: delayed: -2 ≤ Z-score < -1, performance within -1 and -2 SD, Severely delayed: Z-score < -2, performance more than -2 SD.

Discussion

Survival and neonatal morbidity

Of the initial cohort of infants in our study with a birth weight ≤750g, 40.8% (111/272) survived, whereas the survival rate of the infants who were admitted to the NICU was 76% (111/146). Survival rate improved and birth weight increased significantly over the two time periods studied. Although the increasing survival rate is promising, considerable neonatal morbidity persisted. The majority required long-term NICU admission, mechanical ventilation, developed BPD and received hydrocortisone, mostly to wean the infants off the ventilator. Mild intracranial lesions (IVH grade I/II and PVL grade I) were diagnosed in over 65% but severe intracranial lesions (IVH grade III/IV or PVL grade II) were found in only 5%. The low prevalence of severe brain injury in our NICU has also been confirmed in a recent study by Groenendaal et al. who showed that IVH grade III and IV were both diagnosed in 5.7% and cystic PVL was detected in 1.6% in infants (gestational age 25-30 weeks) born between 2002 and 2006. The prevalence of IVH remained unchanged, but cystic PVL significantly decreased over time. Increased antenatal use of antibiotics and nasal CPAP and less mechanical ventilation are suggested as two possible explanations for the decreasing prevalence of cystic PVL.[34] However, these explanations could not be confirmed in our data, looking at a subgroup (≤ 750g) of this population.Withdrawal of intensive care only occurred in 5 of the 146 infants who had been admitted to our NICU during the study period. These 5 infants had severe cerebral lesions (such as intraventricular haemorrhage grade III with severe acute ventricular dilatation of the lateral ventricles or a large unilateral grade IV with a midline shift or bilateral grade IV haemorrhage). Improvement was noted with respect to mechanical ventilation, mainly because ventilation >4 weeks was significantly less often required in cohort II. The significantly lower prevalence of IRDS grade III/IV and BPD is a plausible explanation for the decreased need for prolonged mechanical ventilation and oxygen supply, and an increased use of the infant flow (introduced to the NICU in August 2000) in this cohort. However, the decreased prevalence of IRDS cannot be explained: gestational age was similar in the two cohorts and no differences in administration of prenatal steroids and surfactant was found. Whereas the decreased prevalence of BPD probably resulted from the reduced need for mechanical ventilation in cohort II.

It is also difficult to explain the increased prevalence of hyperbilirubinaemia in cohort II as the gestational age was not significantly different between the two cohorts and there was no difference in the prevalence of IVH.

The significantly shorter gestational age of AGA infants probably resulted in significantly more IRDS, mechanical ventilation >4 weeks, PDA and indomethacin administration. According to our results and results of others it is clear that ELBW infants are prone to severe neonatal morbidities.[6,35,36] However the number of infants with severe respiratory problems who required mechanical ventilation >4 weeks decreased with time.

Neurodevelopmental outcome

Neurodevelopmental outcome in total cohort

Of the 101/111 (91%) children who were assessed at 2 years corrected age, the majority had a normal NDO, 20.8% a mildly and 5% a severely delayed outcome.

Our NDO data are partly in agreement with data presented by others. A review of Lorenz et al. reported a MDI <70 in about 14.3% of the infants with a birth weight ≤800g.[2] However, the percentage of ELBW children with a MDI <70 assessed with the BSID (at 18 to 24 months' of age) ranged from 10.6% to 50%. Hack et al. and Casiro et al. found a MDI <70 in 20% and 23% respectively in infants weighing 500-750g at birth.[1,16] A review of Hack et al. demonstrated a MDI <70 in 13-47% of the children with a birth weight <750-800g.[18] Hack et al. found MDI <70 at 20 month's corrected age in 42% of the children with a birth weight <1000g.[11] In our study population none of the 49 children assessed with the GMDS had a DQ <76 (< -2 SD), whereas 5/52 (9.6%) children assessed with the BSID had a MDI <70.

The lower prevalence of severe developmental delay in our study population compared to other studies most likely results from the guidelines in the Netherlands, stating intensive care should be provided from 25 weeks gestational age onwards. The prevalence of severe brain injury was also low in our population. Intensive care was withdrawn in five infants because of severe cerebral lesions as stated above and this may also have affected the eventual number of infants with severe developmental delay.

Neurodevelopmental outcome over time

NDO was significantly worse in cohort II in comparison with cohort I. In view of the reduced need for ventilation in cohort II, this was an unexpected finding. According to the higher birth weight and the analysis of neonatal morbidity, showing respiratory problems to be less common, we would rather have expected to find an improved outcome for cohort II.

However, the poorer NDO of cohort II may be explained by the higher prevalence of hyperbilirubinaemia. Oh et al. showed that serum bilirubin level directly correlated with impaired NDO.[37]

We furthermore speculate that an explanation for the lower NDO in cohort II might be a difference in ethnical background, parental educational level, SES or differences in obstetrical and neonatal care. However there was no difference in ethnical background between cohort I and II. According to Gross et al. and Weisglas-Kuperus et al., parental educational level, especially of the mother, is an important indicator for NDO.[38,39] In the present study, maternal and paternal educational level was only recorded in respectively 87.1% and 79.2% of the children. 23.9% of the mothers indicated to be a house wife, and these were not included in the analysis. A significantly lower maternal education was found in cohort I (p=0.019), whereas paternal educational level was not significantly different between the two cohorts

(p=0.381). The lower NDO in cohort II could therefore not be explained by parental educational level, however a considerable number of data was missing.
Hille et al. found a 7-fold increase in the need for special education at 9 years of age among children with a low SES, but in our cohort no significant difference in SES between cohort I en II was found (p=0.515).[40]
Schmidt et al. reported that three neonatal morbidities: BPD, brain injury and severe ROP (stage IV and V) strongly predict the risk of neurodisability at 18 months. Since our prevalence of severe ROP is very low i.e. 1% we feel that it is not possible to draw conclusions on the predictive value of presence of severe ROP for neurodisability at 2 years of age in our cohort.[41]
Furthermore, no important differences in perinatal and neonatal care (such as antenatal steroids, number of caesarean sections, use of surfactant, postnatal steroids and HFO) were shown in our data. Nevertheless, due to more active measures in obstetric and neonatal care more severely compromised infants may be kept alive, which may have resulted in a protracted neonatal course with a higher prevalence of neurodevelopmental impairment. Thus, in our population of ELBW infants, an increased survival rate was not accompanied by an improvement in NDO.
Advances in developmental assessments resulted in the use of two different tests. From literature and experience we know that some children perform better on the GMDS, because prolonged attention is required for the BSID-II.[33] Usage of the BSID-II in the majority of cohort II could partly explain the poorer NDO. However, a comparison of the BSID-II and GMDS Z-scores showed no significant difference (Table 3). Furthermore, a pilot study of 29 children with a birth weight <1000g or gestational age <30 weeks, assessed with both the GMDS and BSID at 2 years corrected age confirmed no significant difference between the two tests (p=0.287, unpublished data).
Adverse NDO in ELBW infants is also reported by others. Hack et al. demonstrated similar survival rates and a significant increase in ELBW infants (birth weight <750g) with a MDI <70 at 20 months' corrected age (20% in 1990-1992 to 48% in 1993-1995, p<0.02).[3] Wilson-Costello et al. also showed an increase in children (birth weight 500-749g) with a MDI <70 at 20 month's corrected age (28% in 1982-1989 to 34% in 1990-1998, p=0.529) and a significantly increased survival (27% to 48%, p<0.001).[13]
In contrast to these data, Vohr et al. showed significantly improved survival rates and a significantly decreased MDI <70 rate at 18 months corrected age (birth weight 401-1000g, 29.9% in 1993-1994 to 25.5% in 1995-1996 and 22.8% in 1997-1998, p<0.01).[14] Also a recent study by Wilson-Costello et al. demonstrated a significant decrease in children (birth weight 500-999g) with a MDI <70 at 20 month's corrected age (35% in 1990-1998 to 23% in 2000-2002, p=0.01).[15]
In accordance with other reports on NDO of preterm infants, we too have presented corrected scores. A correction for gestational age is used, as it is implied that

correction for prematurity assists in differentiation between developmental delay associated with prematurity from that caused by brain damage, and results in comparability of NDO of pre-term and full-term infants.[1-3, 11-18, 42-44] However, full correction for prematurity results in a more favourable outcome, as has been noted in our ELBW cohort as well. In our opinion and that of others (Miller et al., Barrera et al. and den Ouden et al.)[42-44] corrected scores overestimate NDO in preterm infants and uncorrected scores better estimate NDO at 2 years of age and more reliably predict future outcome of these children. Moreover, the degree of prematurity of infants admitted to the NICU has increased due to improvement in perinatal and neonatal care. This increased degree of prematurity requiring correction over a wide gestational range may have resulted in reduced reliability of corrected scores. Using corrected scores a poorer NDO of cohort II is shown. However, uncorrected scores NDO scores were lower, but not significantly different between the two cohorts.

Neurodevelopmental outcome in AGA and SGA children

Comparison of AGA and SGA children in our cohort showed a similar survival rate, but significantly more SGA children appeared to have an impaired NDO. An expected finding is the significantly longer gestational age of SGA infants. Previous reports state the major influence of gestational age on survival and it is universally agreed that long term-morbidity increases with decreasing gestational age.[11-14] However, the NDO of our SGA children does not seem to be positively affected by their greater gestational age. The significantly higher percentage of males among SGA children could possibly explain their poorer NDO, as other studies support a better outcome of female children.[45,46]

As male gender was significantly overrepresented in SGA children, gender was tested in a multivariate analysis, but this was not predictive for adverse NDO, neither was delivery by caesarean section.

Furthermore, SES and parental educational level did not differ between SGA and AGA infants. The most plausible explanation is that brain development was adversely affected in these severely growth retarded ELBW infants by chronic intra-uterine malnutrition.

There are only a few recent reports comparing NDO at 2 years corrected age between AGA and SGA ELBW children. Procianoy et al. and Hack et al. found similar BSID-II outcomes for AGA and SGA children (birth weight <1500g and <p10).[47,18] Gortner et al. also found similar GMDS outcomes (SGA <p10).[48] Whereas Anderson et al. found SGA infants (birth weight <p3 and <1000g) to have more cognitive, educational and behavioural impairments.[49] Also Sung et al. demonstrated a poorer performance on the BSID of SGA children (birth weight <p10).[50] Stoelhorst et al. found higher anxious/ depressed and/or withdrawn behaviour at 2 years of age in SGA children (birth weight <p10).[51] Thus, reports on neurodevelopmental performance comparing AGA and SGA children show contradictory results. Moreover, varying definitions of

SGA and differences in neurodevelopmental assessment policy make it difficult to compare our data with other studies.
Limitations of this study include the fact that this was a retrospective analysis, nevertheless we were able to see 91% of the children, born during a 10-year study period, for a neurodevelopmental assessment at 2 years corrected age. All 10 children who were lost to follow-up for the neurodevelopmental assessment in our hospital, survived till 2 years of age. These children were all Caucasian singletons, 40% male and 80% SGA, their neonatal morbidity was comparable to the children who were available for follow-up. An interview of the parents revealed that the main reason for being lost to follow-up was the preference to visit the local pediatrician. We have no reason to suspect that these 10 children would significantly alter our NDO results.
In conclusion, children with a birth weight ≤750g remain at risk for serious neonatal morbidity and adverse NDO. Although survival of these infants increased with time, and the degree of respiratory problems decreased, this was not associated with a better NDO, especially not in SGA children. Long-term follow-up of ELBW infants is essential as they are known to grow into their deficits.

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6

Neurodevelopmental outcome over time of preterm born children ≤ 750 gram at birth

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Abstract

Objectives To describe neurodevelopmental outcome (NDO) at 2, 3.5 and 5.5 years in an extremely low birth weight cohort, to examine the value of NDO at 2 years corrected age (CA) to predict NDO at 3.5 and 5.5 years.

Study design Retrospective cohort study of 101 children with a BW ≤750g born between 1996-2005. NDO was classified as normal (Z-score ≥-1), mildly delayed (-2 ≤ Z-score <-1) or severely delayed (Z-score <-2).

Results At 2, 3.5 and 5.5 years 74.3, 82.2 and 76.2% had a normal NDO. A normal NDO at 2 years CA predicted a normal NDO at 3.5 and 5.5 years in 92% and 84% respectively. Of the children with a mildly or severely delayed NDO at 2 years CA the majority showed an improved NDO at 3.5 (69.2%) and 5.5 years (65.4%) respectively.

Conclusions The majority of the children with a BW ≤750g had a normal NDO at all ages. A normal NDO at 2 years CA is a good predictor for normal outcome at 3.5 and 5.5 years, whereas a delayed NDO at 2 years CA is subject to change with the majority of the children showing a better NDO at 3.5 and 5.5 years.

Introduction

Advances in perinatal medicine have led to a continuous decrease in mortality of extremely low birth weight (ELBW) and extremely preterm infants. In agreement with others, we already reported a significantly increased survival of ELBW infants with a birth weight (BW) ≤750 gram (g) from 65.8% of infants born between 1996 and 2000 to 88.1% when born between 2001 and 2005.[1-5]

It is well known that ELBW infants and extremely preterm born infants are at increased risk of cognitive impairment. Reports on ELBW infants show varying results regarding their neurodevelopmental outcome (NDO). The prevalence of cognitive impairment at 2 years corrected age (CA) ranged between 5% and 50%, and either increased, decreased or remained unchanged over time.[1,3,6-10]

Neurodevelopmental follow-up of ELBW children is essential in order to initiate early intervention to optimize outcome in these children. However, the age for a reliable prediction of NDO in ELBW children differs in the literature. Roth et al. and Vohr et al. showed a good correlation of developmental assessments at one year and school age,[11,12] whereas Weisglas-Kuperus et al. and Hack et al. found a poor correlation between developmental assessments at 2 years compared to 3.5 and 8 years of age respectively.[13,14] Moreover, Astbury et al. and The Victorian Infant Collaborative Study Group found a considerable number of children who improved or deteriorated after 2 years and therefore concluded that an accurate diagnosis of future cognitive abilities is not possible at 2 years.[15,16] In a later paper of The Victorian Infant Collaborative Study Group a good correlation between test results of early childhood and at 14 years are presented, with a normal NDO at 5, 8 and 14 years in 57%, 53% and 59% respectively.[17]

In a more recent study Voss et al.[18] compared the outcome at mean follow-up age of 8.5 years with earlier assessments and found the same developmental classification in 59% at one year, in 68% at two year and in 70% at 3 years of age.

Roberts et al. reported a normal NDO rate of 51.9% and 43.9% at 2 and 8 years of age respectively. They concluded that disability categorisation at 2 years of age had a poor level of agreement with categorisation at 8 years of age (Kappa = 0.20, $p<0.001$).[19]

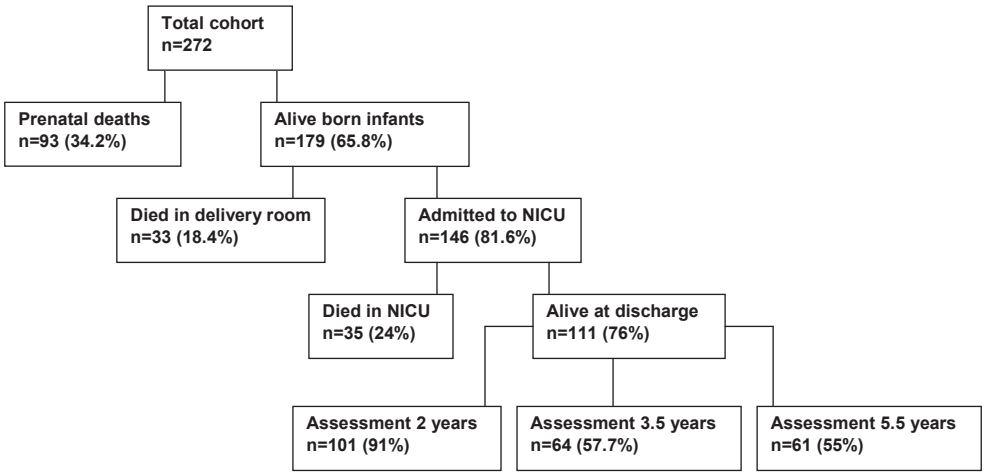
Following our reports on survival, neonatal morbidity and NDO at 2 years of age in infants with a BW ≤ 750g, we now present a retrospective cross-sectional and longitudinal cohort study on NDO of these ELBW children over time.[5,10] The objectives were to describe NDO at 2, 3.5 and 5.5 years of age and to examine the value of NDO at 2 years CA for prediction of NDO at 3.5 and 5.5 years of age. Furthermore, a comparison between two consecutive five-year periods of birth was made and between children who were either appropriate (AGA) or small for gestational age (SGA).

Methods

Subjects

The original study population consisted of a cohort of 272 infants with a BW ≤750g and a gestational age (GA) of ≥24 completed weeks, born in 1996 through to 2000 (cohort I) and 2001 through to 2005 (cohort II). Intra-uterine death occurred in 93 (34.2%) infants and 179 (65.8%) infants were born alive of whom 33 died in the delivery room and 146 infants were admitted to the level three Neonatal Intensive Care Unit (NICU) of the Wilhelmina Children's Hospital Utrecht in the Netherlands. Thirty-five infants died in the NICU. Of the 111 survivors, 101 children (91%) were assessed at 2 years CA, 64 (57.7%) at 3.5 years and 61 (55.0%) at 5.5 years of age (Figure 1). Furthermore, 63 children were assessed at both 2 and 3.5 years of age, 61 at 2 and 5.5 years of age, 46 at 3.5 and 5.5 years and 46 children at 2, 3.5 and 5.5 years of age. The 101 children assessed at 2 years CA form the basis of the analyses presented in this manuscript.

Figure 1. Follow-up of the study population with a birth weight ≤ 750g born between 1996-2005.



Details of ethics approval

All patients admitted to our University Medical Centre do give consent for the use of patient data for scientific research in which their data are processed anonymously. The parents of the study subjects agreed to participate in the neonatal follow-up program of the Wilhelmina Children's Hospital, and gave consent for using these data for scientific research in which their data are processed anonymously.

Data collection and definitions

Data were collected by reviewing the medical charts. GA was based on the last menstrual period and early ultrasound examination. GA categories were classified per week. For example, the category 24 weeks includes a GA of 24 weeks and 0 days till 24 weeks and 6 days. BW percentiles were determined according to the Dutch Perinatal Registry.[20,21] SGA was defined as a BW below the 10th centile.

Parental educational levels were recorded according to the occupational classification standard of Statistics Netherlands.[22] Socio-economic status (SES) was recorded according to the zip code estimated income of The Netherlands Institute for Social Research.[23]

The assessment at 2 years CA consisted of either the Griffiths Mental Developmental Scales (GMDS, n=49) or the Bayley Scales of Infant Development-second edition-Dutch version (BSID-II-NL, n=52), performed by certified investigators. The GMDS consists of five subscales: locomotor, personal-social, hearing-language, eye-hand coordination and performance. This test is designed to yield both global (sum of five subscales) and subscale developmental quotients (DQ) with a mean (±SD) DQ score for the general population of 100 (±12).[24] Assessment of neurodevelopment with the GMDS in our study was based on four subscales excluding locomotion.[2] The BSID-II consists of a Mental Scale and a Psychomotor Scale. The mental developmental index (MDI) was used for neurodevelopmental assessment with a mean of 100 (±SD 15).[26] In case of a MDI <55, 54 was entered in the dataset.

At 3.5 years of age the GMDS was used, and again NDO was based on the above mentioned four subscales. At 3.5 years of age the mean (±SD) DQ score for the general population is 100 (±15).[27]

At 5.5 years of age neurodevelopment was assessed by means of an intelligence test, this was either the Revision Amsterdam Children's Intelligence Test (RAKIT, n=29) or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI, n=18) or the Snijders-Oomen Nonverbal Revised (SON-R, n=5) Intelligence Test.[28-31] A total intelligence quotient (IQ) can be calculated from all three intelligence tests and all have a mean (±SD) score for the general population of 100 (±15). Prior to the appointment for the intelligence test, the parents and teachers of the children were sent the Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF) respectively, and were asked to complete this checklist. The CBCL and TRF are questionnaires assessing syndrome scale scores divided in internalizing and externalizing behaviour. Internalizing behavioural problems consist of the following syndrome scales: emotionally reactive, anxious/ depressed, somatic complaints, withdrawn behaviour and sleep problems. Externalizing problems include attention problems and aggressive behaviour. Furthermore five DSM-oriented scales were assessed for affective, anxiety, pervasive developmental, attention deficit/ hyperactivity and oppositional defiant problems. Subscale T-scores as well as a total T-score were calculated. A normal subscale T-score is defined as below 65, a

borderline T-score as between 65 and 70 and a clinical T-score as more than 70. For internalizing, externalizing and total problems scales a normal score is defined as below 60, borderline clinical range as between 60 and 63 and clinical range as more than 63.[32]
Furthermore, at 5.5 years of age the school type (regular or special education) was registered.
Developmental scores at 2 years of age were calculated for CA. A correction for prematurity was made by subtracting the amount of prematurity (40 minus GA at birth) from the actual age at testing. NDO at 3.5 and 5.5 years of age were computed for uncorrected age (UCA).
Z-scores were calculated for all neurodevelopmental scores in order to compare NDO at 2, 3.5 and 5.5 years of age. NDO was classified as normal (Z-score ≥-1), mildly delayed (-2 ≤ Z-score < -1) and severely delayed (Z-score < -2).

Statistical analysis
To check for accuracy, data entered were double checked. All analyses were performed using SPSS version 15.0. Statistical comparisons for continuous variables were made with Mann-Whitney tests. Dichotomous and categorical variables were tested using Chi-square test or Fisher's exact test. A p value <0.05 was considered to be statistically significant.
Comparisons of NDO at different test ages were expressed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Furthermore, to examine the predictive value of the classification of NDO between the three test ages the C-statistic for discrimination was derived from Somer's D. A C-Statistic of 0.6 to 0.7 is generally considered to be of limited value, 0.7 to 0.8 has modest value, and values greater than 0.8 are considered to have discrimination adequate for genuine clinical utility.[33]
Various subjects had missing values for NDO at 3.5 years and 5.5 years of age. Exclusion of the subjects with missing values yields biased results as children who are lost to follow-up are often selectively missing, which also seemed to be the case in our study (Table 6). Hence, we imputed missing values by single imputation.[34,35]

Results

Baseline characteristics
Table 1 shows the baseline characteristics of the 101 children who have been assessed at 2 years CA. The median BW was 675g and median GA was 28 weeks. A significantly higher BW was noted in cohort II (685g versus 649g, p=0.025). The median GA of both cohorts I and II was 28 weeks. SGA infants had a significantly lower BW than AGA infants (635g versus 720g, p<0.001), whereas a significantly shorter GA was found in AGA infants (26.7 versus 28.8 weeks, p<0.001). All SGA infants were delivered by caesarean section compared to 60% of the AGA infants (p<0.001).

Table 1. Characteristics of 101 surviving children assessed at 2 years of age, total cohort, cohort I and II, AGA and SGA infants.

	By cohort				By GA		
	Total cohort n=101	Cohort I n=45	Cohort II n=56	Cohort I vs II	AGA n=45	SGA n=56	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Median maternal age (years) (min-max)	30.0 (17-45)	29.0 (19-43)	31.0 (17-45)	0.198	29.0 (19-43)	31.0 (17-45)	0.173
Median birth weight (gram) (min-max)	675 (480-750)	649 (480-750)	685 (540-750)	**0.025**	720 (580-750)	635 (480-750)	**<0.001**
Median GA (weeks) (min-max)	28.00 (24.84-34.42)	27.84 (24.84-34.42)	28.21 (25.0-34.14)	0.205	26.70 (24.84-29.42)	28.84 (26.28-34.42)	**<0.001**
Multiple birth	20 (19.8)	8 (17.8)	12 (21.4)	0.803	13 (28.9)	7 (12.5)	**0.048**
Male	45 (44.6)	20 (44.4)	25 (44.6)	1.000	15 (33.3)	30 (53.6)	**0.047**
Ethnicity (Caucasian)	93 (92.1)	43 (95.6)	50 (89.3)	0.293	40 (88.9)	53 (94.6)	0.461
SES				0.515			0.429
-High	21 (21.0)	7 (15.6)	14 (25.5)		9 (20.5)	6 (10.7)	
-Average	64 (64.0)	31 (68.9)	33 (60.0)		26 (59.1)	38 (67.9)	
-Low	15 (15.0)	7 (15.6)	8 (14.5)		9 (20.5)	12 (21.4)	
Maternal educational level				**0.019**			0.308
-High	12 (17.9)	1 (3.3)	11 (29.7)		5 (15.6)	7 (20.0)	
-Average	28 (41.8)	14 (46.7)	14 (37.8)		11 (34.4)	17 (48.6)	
-Low	27 (40.3)	15 (50.0)	12 (32.4)		16 (50.0)	11 (31.4)	
Prenatal steroids (GA <32 w)	81 (86.2)	34 (82.9)	47 (88.7)	0.549	39 (86.7)	42 (85.7)	1.000
Caesarean delivery	83 (82.2)	36 (80.0)	47 (83.9)	0.794	27 (60.0)	56 (100)	**<0.001**
5–min Apgar score <7	12 (11.9)	6 (13.3)	6 (10.7)	0.762	8 (17.8)	4 (7.1)	0.127
SGA	56 (55.4)	22 (48.9)	34 (60.7)	0.314	-	-	-

Total cohort: children born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, GA: gestational age, SGA: small for gestational age <p10. AGA: appropriate for gestational age ≥p10, SES: socio-economic status, Maternal educational level was available in 87.1% (23.9% indicated to be a house-wife, analyses performed on n=67).

Neurodevelopmental outcome at 2 years corrected age
NDO at 2 years CA of 101 children is presented in Table 2. The mean age at testing was 23 months (SD 2). These children were assessed by means of either the GMDS (n=49) or the BSID-II-NL (n=52). No significant differences were noted between the corrected Z-scores of the GMDS and BSID-II-NL (p=0.661).[10] 74.3% of the children had a normal NDO, 20.8% a mildly delayed and 5% a severely delayed outcome.
A normal NDO was significantly more often found in AGA children (86.7% versus 64.3% in SGA, p=0.012).

Neurodevelopmental outcome at 3.5 years of age
NDO at 3.5 years of age is presented in Table 2. These children were all assessed by means of the GMDS. The mean age at testing was 41.4 months (SD 2.9): 82.2% of the children had a normal NDO, 15.8% a mildly delayed and 2% a severely delayed outcome. No significant differences were noted between AGA and SGA children.

Intelligence and behaviour at 5.5 years of age
The results of the intelligence tests at 5.5 years of age are shown in Table 2. The mean age at testing was 5.9 years (SD 1.1). In the majority (76.2%) NDO was classified as normal, 16.8% as mildly delayed and 6.9% as severely delayed. No significant differences in intelligence were noted between AGA and SGA children.
School type was available for 88/101 (87.1%) children. 17/88 (19.3%) children needed special education, this was not significantly different between AGA and SGA children (18.4% and 20% respectively, p=1.000). The main reason for referral to special education was the presence of hearing and speech problems.
Behavioural assessment by means of the CBCL and TRF was completed by 47 of the parents and 43 of the teachers respectively. The total scores of internalizing and externalizing behavioural problems are presented in Table 3. The majority of the children were reported to have a normal behaviour according to their parents (83%) and teachers (88.4%). No significant differences in behaviour were noted between AGA and SGA children.

Comparison of cohort I and II
Comparison of cohort I and II revealed that significantly more children in cohort I had a normal NDO at 2 years CA (84.4% versus 66.1%, p=0.042), fewer had a mildly delayed (15.6% versus 25%) and none had a severely delayed performance versus 8.9% in cohort II.
At 3.5 years of age significantly more children in cohort I performed within normal limits (91.1% versus 75.0%, p=0.040), fewer had a mildly delayed (8.9% versus 21.4%) and none had a severely delayed performance versus 3.6% in cohort II.
At 5.5 years of age no significant differences in intelligence and behaviour were noted between cohort I and II.

Table 2. Neurodevelopmental outcome of 101 children at 2, 3.5 and 5.5 years of age.

	By cohort				By GA		
	Total cohort n=101	Cohort I n=45	Cohort II n=56	Cohort I vs II	AGA n=45	SGA n=56	AGA vs SGA
				p-value			p-value
NDO 2 years CA							
Mean Z-score	-0.37	-0.20	-0.50	0.164	-0.15	-0.54	0.050
SD (min~max)	1.0 (-3.07~2.23)	(0.8, -1.69~2.23)	(1.2, -3.07~1.87)		1.0 (-3.07~2.23)	1.0 (-2.80~1.87)	
Normal, n (%)	75 (74.3)	38 (84.4)	37 (66.1)	0.051	39 (86.7)	36 (64.3)	**0.020**
Mildly delayed, n (%)	21 (20.8)	7 (15.6)	14 (25.0)		4 (8.9)	17 (30.4)	
Severely delayed, n (%)	5 (5.0)	0	5 (8.9)		2 (4.4)	3 (5.4)	
NDO 3.5 years							
Mean Z-score	-0.53	-0.41	-0.52	0.205	-0.45	-0.60	0.449
SD (min~max)	0.6 (-3.21~1.03)	0.5 (-1.94~1.03)	0.7 (-3.21~0.41)		0.5 (-1.59~0.41)	0.7 (-3.21~1.03)	
Normal, n (%)	83 (82.2)	41 (91.1)	42 (75.0)	0.090	38 (84.4)	45 (80.4)	0.706
Mildly delayed, n (%)	16 (15.8)	4 (8.9)	12 (21.4)		7 (15.6)	9 (16.1)	
Severely delayed, n (%)	2 (2.0)	0	2 (3.6)		0	2 (3.6)	
NDO 5.5 years							
Mean Z-score	-0.38	-0.46	-0.32	0.657	-0.35	-0.41	0.853
SD (min~max)	1.1 (-3.47~2.13)	1.1 (-3.47~1.40)	1.0 (-2.40~2.13)		1.1 (-3.47~2.13)	1.0 (-3.47~1.47)	
Normal, n (%)	77 (76.2)	34 (75.6)	43 (76.8)	1.000	35 (77.8)	42 (75.0)	0.938
Mildly delayed, n (%)	17 (16.8)	8 (17.8)	9 (16.1)		7 (15.6)	10 (17.9)	
Severely delayed, n (%)	7 (6.9)	3 (6.7)	4 (7.1)		3 (6.7)	4 (7.1)	

Total cohort: children born in 1996-2005, cohort I: born in 1996-2000, cohort II: born in 2001-2005. AGA: appropriate for gestational age: birth weight (BW) ≥ p10, SGA: small for gestational age: BW <p10. NDO: neurodevelopmental outcome. 2 year: Griffiths Mental Development Scales (GMDS), Developmental Quotient (DQ), locomotor (LM) subscale excluded or Bayley Scales of Infant Development-II-NL, Mental Developmental Index (MDI). 3.5 year: GMDS DQ LM subscale excluded. 5.5 year: IQ measured with RAKIT, WPPSI or SON-R intelligence test. CA: corrected age. Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2. For missing values of NDO at 3.5 and 5.5 years of age single imputation was used.

Table 3. Behavioural assessment at 5.5 years of age.

		By cohort			By GA		
	Total cohort n=47	Cohort I n=13	Cohort II n=34	Cohort I vs II	AGA n=20	SGA n=27	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
CBCL parents							
Normal	39 (83.0)	10 (76.9)	29 (85.3)	0.219	14 (70.0)	25 (92.6)	0.144
Borderline clinical range	5 (10.6)	3 (23.1)	2 (5.9)		4 (20.0)	1 (3.7)	
Clinical range	3 (6.4)	0	3 (8.8)		2 (10.0)	1 (3.7)	
	Total cohort n=43	Cohort I n=11	Cohort II n=32	Cohort I vs II	AGA n=20	SGA n=23	AGA vs SGA
	n (%)			p-value	n (%)	n (%)	p-value
TRF teacher							
Normal	38 (88.4)	11 (100)	27 (84.4)	0.671	17 (85.0)	21 (91.3)	0.323
Borderline clinical range	1 (2.3)	0	1 (3.1)		0	1 (4.3)	
Clinical range	4 (9.3)	0	4 (12.5)		3 (15.0)	1 (4.3)	

Total cohort: children born in 1996-2005, cohort I: born in 1996-2000, cohort II: born in 2001-2005. AGA: appropriate for gestational age: birth weight (BW) ≥ p10, SGA: small for GA: BW < p10, Behaviour based on total problems (externalizing and internalizing) of Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF) completed by the parents and teachers respectively. A normal score is defined as <60, borderline clinical range as between 60-63 and clinical range as > 63.

Neurodevelopmental outcome over time

In summary, cross-sectional data showed that the majority of the children had a normal NDO at the three test ages (74.3%, 82.2% and 76.2% respectively).

Comparison of 2 and 3.5 years of age

Of the children with a normal NDO at 2 years CA, 69/75 (92%) also had a normal outcome at 3.5 years of age, whereas 6/75 (8%) deteriorated to a mildly delayed NDO. Of the children who were mildly delayed at 2 years CA, 6/21 (28.6%) remained mildly delayed at 3.5 years, 13/21 (61.9%) improved to a normal NDO and 2/21 (9.5%) deteriorated to the severely delayed category. As for the 5 severely delayed children at 2 years CA, 4 children improved to a mildly delayed category at 3.5 years of age and one to a normal NDO. Furthermore, 18/26 (69.2%) children with a mildly or severely delayed NDO at 2 years CA showed an improved NDO at 3.5 years of age. So, altogether 75/101 children (74.3%) remained in the same category at 2 and 3.5 years of age. The C-statistic of 0.69 showed a reasonable predictive value of NDO at 2 years CA for the outcome at 3.5 years (Table 4a). The sensitivity for normal outcome at both 2 and 3.5 years was 83.1% with a PPV of 92%, and the specificity for abnormal outcome (mildly and severely delayed) at both ages was 66.7% with a NPV of 46.2% (Table 5).

Comparison of 2 and 5.5 years of age

Of the children with a normal NDO at 2 years CA 63/75 (84%) also had a normal outcome at 5.5 years, 11/75 (14.7%) deteriorated to a mildly delayed NDO and one child to the severely delayed category. Of those with a mildly delayed NDO 2 years CA, 3/21 (14.3%) remained in the same category at 5.5 years of age, whereas 13/21 (61.9%) improved to a normal NDO and 5/21 (23.8%) deteriorated to a severely delayed NDO. As for the five severely delayed children at 2 years CA, one child remained severely delayed, 3 improved to a mildly delayed NDO and one child improved to a normal NDO at 5.5 years of age. Furthermore, 17/26 (65.4%) children with a mildly or severely delayed NDO at 2 years CA showed an improved NDO at 5.5 years of age. So, 67/101 children (66.3%) remained in the same category at 2 and 5.5 years of age. The C-statistic of 0.67 showed a reasonable predictive value of the NDO at 2 years CA for the outcome at 5.5 years of age (Table 4b). The sensitivity and PPV for normal outcome was 81.8% and 84% respectively, and the specificity and NPV for abnormal outcome was 50% and 75% respectively (Table 5).

Comparison of 3.5 and 5.5 years of age

Of the children with a normal NDO at 3.5 years of age 68/83 (81.9%) children also had a normal outcome at 5.5 years of age. 11/83 (13.3%) deteriorated to the mildly delayed category and 4/83 (4.8%) to the severely delayed one. Of the children with a mildly delayed NDO at 3.5 years of age, 6/16 (37.5%) remained mildly delayed at 5.5

years of age, 3/16 (18.8%) children deteriorated to the severely delayed category and 7/16 (43.8%) improved to normal. Furthermore, 9/18 (50%) children with a mildly or severely delayed NDO at 3.5 years CA showed an improved NDO at 5.5 years of age. So, 74/101 children (73.3%) remained in the same category at 3.5 and 5.5 years of age. The C-statistic of 0.65 showed a reasonable predictive value of the NDO at 3.5 years of age for the outcome at 5.5 years of age (Table 4c). The sensitivity for normal outcome was 88.3% with a PPV of 81.9%, and the specificity for abnormal outcome at both ages was 37.5% with a NPV of 50% (Table 5).

Table 4a. Classification of neurodevelopmental outcome at 2 and 3.5 years of age in 101 ELBW children.

Classification of NDO at 2 y	Classification of NDO at 3.5 y, n (%)			
	Normal	Mildly delayed	Severely delayed	Total, n (%)
Normal	69 (92.0) [a]	6 (8.0) [c]	0	75 (74.3)
Mildly delayed	13 (61.9) [b]	6 (28.6) [a]	2 (9.5) [c]	21 (20.8)
Severely delayed	1 (20.0) [b]	4 (80.0) [b]	0	5 (5.0)
Total, n (%)	83 (82.2)	16 (15.8)	2 (2.0)	101 (100)

Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2.
Percentages are row percentages, except for the totals for 2 years, which are column percentages.
[a] unchanged, [b] improved, [c] deteriorated. For missing values of NDO at 3.5 years of age single imputation was used. C-statistic = 0.693 95% confidence interval (CI) [0.598-0.787].

Table 4b. Classification of neurodevelopmental outcome at 2 and 5.5 years of age in 101 ELBW children.

Classification of NDO at 2 y	Classification of NDO at 5.5 y, n (%)			
	Normal	Mildly delayed	Severely delayed	Total, n (%)
Normal	63 (84.0) [a]	11 (14.7) [c]	1 (1.3) [c]	75 (74.3)
Mildly delayed	13 (61.9) [b]	3 (14.3) [a]	5 (23.8) [c]	21 (20.8)
Severely delayed	1 (20.0) [b]	3 (60.0) [b]	1 (20.0) [a]	5 (5.0)
Total, n (%)	77 (76.2)	17 (16.8)	7 (6.9)	101 (100)

Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2.
Percentages are row percentages, except for the totals for 2 years, which are column percentages.
[a] unchanged, [b] improved, [c] deteriorated. For missing values of NDO at 5.5 years of age single imputation was used. C-statistic = 0.670 95% CI [0.570-0.770].

Neurodevelopmental outcome per GA

In Figure 2a, 2b and 2c the results of our analysis of the NDO per GA subgroups are shown. Children with a mildly or severely delayed outcome are especially found in the upper GA categories, indicating a poorer NDO for extreme SGA children. It should however be noted that some GA subgroups are represented by small numbers of children.

Table 4c. Classification of neurodevelopmental outcome at 3.5 and 5.5 years of age in 101 ELBW children.

Classification of NDO at 3.5 y	Classification of NDO at 5.5 y, n (%)			
	Normal	Mildly delayed	Severely delayed	Total, n (%)
Normal	68 (81.9) [a]	11 (13.3) [c]	4 (4.8) [c]	83 (82.2)
Mildly delayed	7 (43.8) [b]	6 (37.5) [a]	3 (18.8) [c]	16 (15.8)
Severely delayed	2 (100) [b]	0	0	2 (2.0)
Total, n (%)	77 (76.2)	17 (16.8)	7 (6.9)	101 (100)

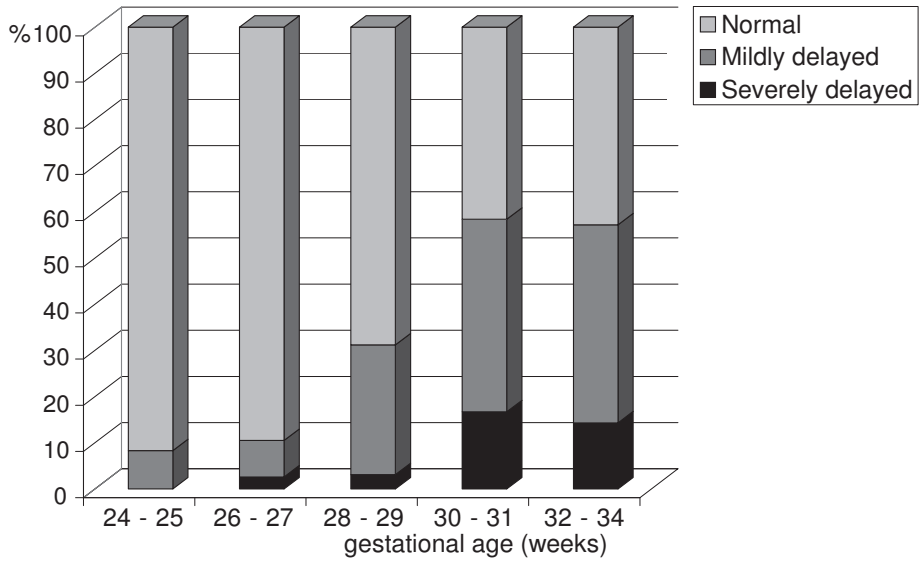
Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2.
Percentages are row percentages, except for the totals for 3.5 years, which are column percentages.
[a] unchanged, [b] improved, [c] deteriorated. For missing values of NDO at 3.5 years and 5.5 years of age single imputation was used. C-statistic = 0.654 95% CI [0.530-0.777].

Table 5. Predictive value of neurodevelopmental outcome at 2, 3.5 and 5.5 years of age.

	Sensitivity	Specificity	PPV	NPV
	%	%	%	%
2 for 3.5 years	83.1	66.7	92.0	46.2
2 for 5.5 years	81.8	50	84	75
3.5 for 5.5 years	88.3	37.5	81.9	50

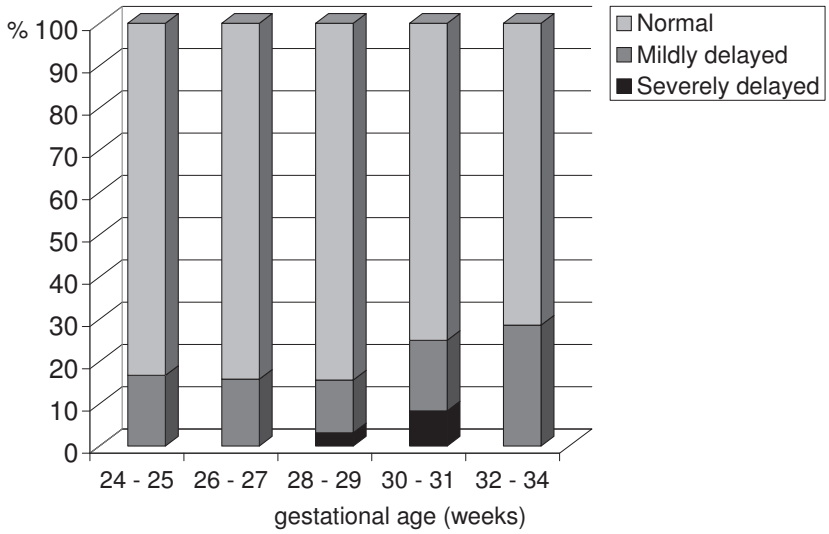
PPV: positive predictive value, NPV: negative predictive value.

Figure 2a. Neurodevelopmental outcome at 2 years per GA (n=101).



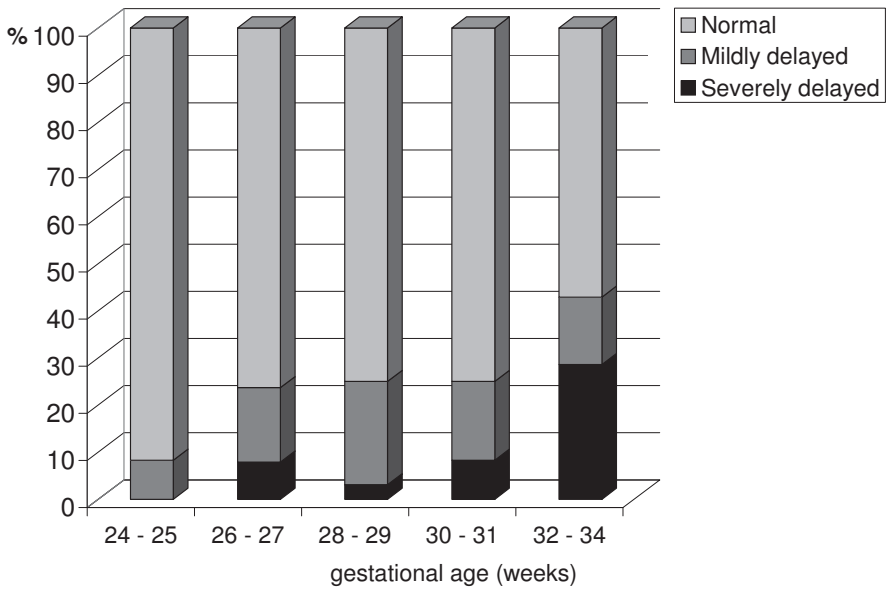
NDO assessed with GMDS or BSID-II-NL. 24-25: n=12, 26-27: n=38, 28-29: n=32, 30-31: n=12, 32-34: n=7. Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2.

Figure 2b. Neurodevelopmental outcome at 3.5 years per GA (n=101).



NDO assessed with GMDS. 24-25: n=12, 26-27: n=38, 28-29: n=32, 30-31: n=12, 32-34: n=7. Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2.

Figure 2c. Neurodevelopmental outcome at 5.5 years per GA (n=101).



NDO assessed with intelligence test. 24-25: n=12, 26-27: n=38, 28-29: n=32, 30-31: n=12, 32-34: n=7. Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2.

Discussion

Our study population of ELBW children ≤ 750g is known to be at risk for cognitive impairment. However, the majority of the children had a normal NDO at 2, 3.5 and 5.5 years of age (74.3%, 82.2% and 76.2% respectively).

Neurodevelopmental outcome at 2 years corrected age

Reports on impaired neurodevelopment of ELBW children at 2 years CA are abundant, but varying greatly from 5% to 50%.[1,3,6-10] However, literature presenting the data of a normal NDO at 2 years CA in these children is limited, but also varies over a substantial range from 29.5% to 66%.[2,4,36-39] Comparing these data with ours demonstrated a better performance of our ELBW population with a normal NDO of 74.3% at 2 years CA. Only the data of Spinillo et al. showed more promising results of an unimpaired 2 year NDO of 78.4% in a cohort of infants delivered at 24 to 33 weeks gestation between 1990 to 2004.[40] However, due to differences in the developmental assessments used and perinatal characteristics such as GA and neonatal morbidities of the cohorts studied comparison remains difficult.

Despite increased survival of the children born between 2001-2005, NDO was significantly worse in cohort II in comparison with cohort I. In view of the higher BW, reduced prevalence of respiratory problems and the reduced need for ventilation in cohort II, we would rather have expected to find an improved outcome for cohort II. However, the poorer NDO of cohort II may be explained by the higher prevalence of hyperbilirubinaemia.[10] Oh et al. showed that higher peak serum bilirubin levels directly correlated with impaired NDO.[41] No important differences in perinatal and neonatal care (such as antenatal steroids, number of caesarean sections, use of surfactant, postnatal steroids and HFO) were shown in our data. Nevertheless, due to more active measures in obstetric and neonatal care more severely compromised infants may be kept alive, which may have resulted in a protracted neonatal course with a higher prevalence of neurodevelopmental impairment.

Advances in developmental assessments resulted in the use of two different tests (GMDS and BSID-II). From the literature and our own experience we know that some children perform better on the GMDS, because prolonged attention is required for the BSID-II.[26] The use of the BSID-II in the majority of cohort II could partly explain the poorer NDO. However, a comparison of the BSID-II and GMDS Z-scores showed no significant difference.[10]

Neurodevelopmental outcome at 3.5 years of age

Recent literature on normal NDO of ELBW children at 3.5 years of age is scarce, and the data found ranged from 44% to 77% in cohorts of ELBW and VLBW children.[13,42-45] The more recent literature shows poorer NDO in low BW children, this most likely results from the decreasing GA of surviving infants. Compared to other reports, our ELBW cohort showed a better NDO at 3.5 years of age (normal NDO in 82.2%),

even when comparing with VLBW cohorts.[13,44]
At 3.5 years of age, as well as at 2 years CA, significantly fewer children in cohort II achieved a normal NDO. The same explanations as described above may account for this finding. However, at 3.5 years of age all children were assessed with the GMDS.

Neurodevelopmental and behavioural outcome at 5.5 years of age
At 5.5 years of age a normal IQ was found in the majority (76.2%) of our ELBW cohort. At 5.5 years of age, the NDO of cohort I and II did not differ anymore. Possible explanations could be the delayed maturation of extremely preterm born ELBW children. However, median GA was not different between cohort I and II and the median BW was even higher in cohort II. It is therefore more likely that a more correct estimation of NDO can be obtained at older ages, when the performance of these children is less affected by shyness and fear. Furthermore, usage of an actual intelligence test instead of a developmental test may have accounted for this finding as well.
A normal NDO at 5 years of age in ELBW and preterm children reported by others ranged from 26% to 78%.[47-53] The need for special education shown by others was rather high and varied from 43% to 51% in preterm ELBW cohorts.[47,48,53] Furthermore, Steinmacher et al. found behavioural and attention problems in 6% and 12% respectively in a cohort of preterm infants (GA 23-25 weeks).[53] These data are in agreement with the clinical behavioural problems reported by the parents and teachers in our cohort (6.4% and 9.3% respectively). Others showed significantly more behavioural problems (higher parent and teacher ratings) in extremely preterm born and VLBW children compared to their term-born peers.[54-56]

Neurodevelopmental outcome over time
The majority of the children with a normal NDO at 2 years CA also had a normal outcome at 3.5 and 5.5 years of age. The greater part of the children classified as mildly or severely delayed at 2 years CA had a better NDO at 3.5 and 5.5 years of age and only a few children got a more worse NDO. Therefore a high sensitivity and PPV were found but a poorer specificity and NPV.
Bowen et al. assessed ELBW children (born between 1985-1988, BW 500-999g) at 3 and 5 years (GMDS and IQ test respectively). They found NDO at 3 years to be a good predictor for intelligence at 5 years.[57] Gianni et al. compared NDO at 2 and 3.5 years in ELBW infants born between 1996 and 2001. NDO remained unchanged in 76.6%, improved in 5% and deteriorated in 18.4%.[46] The high percentage of deteriorating development in this study is remarkable compared to the 7.9% in the present study. Possibly the presence of a low SES and low maternal education level in 28.9% of their ELBW cohort may have accounted for this.
Marlow et al. reported that severe developmental delay at 30 months was highly

predictive for outcome at 6 years (GA < 26 weeks, born in 1995). Of the 63 children classified as having a severely delayed development at 30 months, 86% had either severe or moderate developmental delay at 6 years. The category of a severely delayed development at 30 months had low sensitivity (50%) for moderate or severe disability at 6 years but good specificity (93%).[51] Hack et al.[14] found that a normal outcome at 20 months CA correlated well with a normal outcome at 8 years of age (predictive value 0.99, ELBW infants born between 1992-1995.), contrary to the findings of Roberts et al.[19] who reported a normal NDO in 51.9% and 43.9% at 2 and 8 years of age respectively (BW 500-999g and GA 22-27 weeks, born in 1997), and the overall rate of children with a severe developmental delay increased between 2 and 8 years of age[19] Astbury et al. found that impairment was underestimated at one year of age and developmental delay was overestimated at two years of age in children with a BW ≤ 1000g born between 1979 and 1981. They concluded that reliable estimation of cognitive abilities of ELBW infants is not possible until school age.[15] The Victorian Infant Collaborative Study Group found that in 73.6% the NDO at 2 and 5 years of age was similar, but 15.4% deteriorated and 11.1% improved. The authors suggest that 2 years is too early to reliably estimate the neurosensory outcome of ELBW children.[16,17] In contrast, Voss et al. showed that the minimum age for reliable developmental prognosis is 2 years CA, with a correct prognosis in 68% compared to the outcome at 8.5 years of age. At 4 years of age the predictive value was only slightly better with a correct prognosis in 70%.[18]

Johnson et al. showed that neurodevelopmental disability remained stable between 6 and 11 years of age (serious disability in 42% and 45% respectively) in preterm born children (GA < 26 weeks born in 1995).[58]

As shown by our data and the studies cited above, NDO of ELBW children is subject to change in about a quarter of studied cohorts in early childhood. In the literature on NDO of ELBW infants, there is no consensus on the age at which a child's development can be reliably predicted.

However, we may conclude that children who are classified as normal in early infancy, most likely remain in this category, but 2 years of age is probably too early for a fixed diagnosis of a mildly or severely delayed development in ELBW infants. A possible explanation of an incorrectly estimated (i.e. worse) developmental prognosis of ELBW infants at earlier ages could be brain plasticity during childhood as suggested by Luciana.[59]

Neurodevelopmental outcome per gestational age

A mildly or severely delayed outcome is especially found in the ELBW children born at the upper GA subgroups, indicating a poorer NDO for extreme SGA children. The most plausible explanation is that brain development was adversely affected in these severely growth retarded ELBW children by chronic intra-uterine malnutrition. Interesting is that the significantly poorer NDO in SGA children noted at 2 years CA

was no longer present at 3.5 and 5.5 years of age. The use of two developmental tests with different tasks at 2 years CA may have affected these results.[24,26,27] However, no significant differences were noted between the corrected Z-scores of the GMDS and BSID-II-NL. We assume that brain plasticity might be a possible explanation for this finding.[59] Anderson et al. and van Wassenaer also found ELBW SGA infants to have more cognitive, educational and behavioural impairments at this early age.[50,60]

To appreciate the presented results, some issues need to be addressed.
In our study the neurodevelopmental assessment at the ages of 2, 3.5 and 5.5 years took place during, or in combination with, follow-up visits to the neonatologist. However, as can be seen from Figure 1, not all children did undergo the assessment at each of the time points. We speculate about potential reasons for loss to follow-up in this cohort. One reason might be that the children were doing well and hence the parents did not feel the need for a visit to the follow-up clinic. Another reason might be that children were having problems and an intervention program was already initiated by the local paediatrician. Other possible explanations for the loss to follow-up are that parents decided to discontinue the hospital check-ups (independent of the condition of their child) after the many hospital visits in early infancy, or because they preferred to visit the local paediatrician rather than travel the distance to our university hospital.
Altogether, at 2 years CA we were able to see 101/111 children (91%) for follow-up. The 10 children lost to follow-up before this time point all survived till 2 years of age, were all Caucasian singletons, 40% male and 80% SGA, and their neonatal morbidity was comparable to the children who were available for follow-up. The major reason for being lost to follow-up was the preference to visit the local paediatrician. We have no reason to suspect that these 10 children would significantly alter our NDO results.
At 3.5 years of age we were able to see 64 out of the 101 children (63.4%) for the neurodevelopmental assessment. In 37 children NDO was missing; for three of them the GMDS could not be completed due to lack of cooperation of the child. Of the remaining 18/34 children, the GMDS was not used by one of our neonatologists due to unfamiliarity with the test. However, his notes described a normal development in these 18 children. Unfortunately, 16 children were lost to follow-up at 3.5 years of age because of the above mentioned reasons.
An additional analysis in our data showed that 81.1% (30/37) of the children who had not been assessed at 3.5 years of age had a normal NDO at 2 years CA. Therefore, the NDO results at 3.5 years of age of 64 children might be biased and underestimated due to the lost to follow-up of children who were doing well at 2 years CA. This assumption is supported by our finding that 92% of the children who had a normal NDO at 2 years CA also had a normal NDO at 3.5 years of age.
We compared the baseline characteristics, neonatal complications and NDO at 2 years CA between the non-missing and missing children (Table 6). Children who

were lost to follow-up had a lower BW, bronchopulmonary dysplasia (BPD) was more common and mechanical ventilation was required more often in these children. Important indicators for NDO like maternal education and socio-economic status were not significantly different. However, considering the influence of a lower BW and a higher prevalence of BPD on NDO, we assume that the NDO at 3.5 years of age based on 64 children potentially overestimated their performance.[1-4,61] Therefore, we decided to perform a single imputation missing value analysis. As a sensitivity analysis we compared these results with the results of the 64 children who actually had been assessed 3.5 years of age and found no major differences (normal NDO in 82.8% and 82.2% respectively). Still with or without imputation NDO at 3.5 years of age is more favourable compared to the outcome data at 2 years CA and 5.5 years of age. The norms of the GMDS are rather out-dated and therefore the development of the children assessed with the GMDS might have been overestimated.[24,27]

At 5.5 years of age an IQ test had been performed in 61 children. At present, 8 children are not yet 5.5 years of age. Since 2004, the follow-up of children aged 5.5 years and older has improved, as an IQ test at 5.5 years of age has since then become a regular part of standard follow-up of all children. An analysis of the children who were 5.5 years of age from 2004 onwards revealed a more acceptable follow-up of 52/71 (73.2%).

As an approximation for the neurodevelopmental condition of the children, we inquired all parents for the school type of their child at 5.5 years of age. We succeeded to obtain this information for 88/101 (87.1%) children. We found that the percentage of children that attended a regular school was not significantly different between the 61 children in whom an IQ test was performed and the 27 without IQ data (80.3% versus 81.5% respectively, p= 1.000). However, the above mentioned possible bias in case of missing values is also present for the NDO data at 5.5 years of age. Therefore, the missing value analysis, as described above was also performed for the NDO results at 5.5 years of age. As a sensitivity analysis we also compared these results with the results of the 61 children who actually had been assessed 5.5 years of age and found no major differences (normal NDO in 76.2% and 75.4% respectively).

Conclusion

In conclusion, ELBW children are at risk for cognitive impairment. However, in our study population the majority of the children with a BW ≤ 750g had a normal NDO at 2, 3.5 and 5.5 years of age. SGA children born at the upper GA categories exhibited the worst outcome at all test ages. A normal NDO at the age of 2 quite accurately predicts the NDO at 3.5 years and 5.5 years of age. A delayed future NDO cannot be reliable predicted at 2 years of age, as development of these ELBW children is still highly subject to change. Therefore, we suggest a change in emphasis of the ELBW children who definitely require long term follow-up: for the children who show a mildly or severely delayed NDO at the age of 2, long-term follow-up should be

strongly recommended. For the children who show a normal NDO at 2 years CA, longer follow-up may be less essential, although still recommended.
Nevertheless, parents should be informed and realize that their ELBW child is at increased risk of behavioural and social-emotional problems, and therefore any support necessary should be easy accessible.

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Table 6. Characteristics of missing versus non-missing NDO data at 3.5 years of age.

	Missing n=37 n (%)	Non-missing n=64 n (%)	Missing vs non-missing p-value
Median maternal age (years) (min-max)	29 (19-43)	30.5 (17-45)	0.489
Median birth weight (gram) (min-max)	640 (480-750)	690 (530-750)	**0.011**
Median gestational age (weeks) (min-max)	27.7 (25.0-34.4)	28.1 (24.8-32.8)	0.234
Multiple birth	8 (21.6)	12 (18.8)	0.798
Male	14 (37.8)	31 (48.4)	0.406
Ethnicity (Caucasian)	33 (89.2)	60 (93.8)	0.460
SES			0.912
-high	7 (18.9)	14 (22.2)	
-average	24 (64.9)	40 (63.5)	
-low	6 (16.2)	9 (14.3)	
Maternal educational level			0.138
-high	2 (7.1)	10 (25.6)	
-average	14 (50.0)	14 (35.9)	
-low	12 (42.9)	15 (38.5)	
Prenatal steroids (GA <32 weeks)	29 (87.9)	52 (85.2)	1.000
Caesarean delivery	30 (81.1)	53 (82.8)	1.000
5-min Apgar score <7	5 (13.5)	7 (10.9)	0.755
SGA	18 (48.6)	38 (59.4)	0.308
NICU admission > 28 days	33 (89.2)	54 (84.4)	0.565
Mechanical ventilation			
-no	3 (8.1)	17 (26.6)	**0.013**
-short (< 2 weeks)	8 (21.6)	21 (32.8)	
-intermediate (≥ 2 to 4 weeks)	16 (43.2)	20 (31.3)	
-long (> 4 weeks)	10 (27.0)	6 (9.4)	
Oxygen	36 (97.3)	56 (87.5)	0.149

	Missing n=37	Non-missing n=64	Missing vs non-missing
	n (%)	n (%)	p-value
IRDS			0.256
-no	12 (32.4)	31 (48.4)	
-grade I/II	11 (29.7)	17 (26.6)	
-grade III/ IV	14 (37.8)	16 (25.0)	
BPD	27 (73.0)	30 (46.9)	**0.013**
Hypotension	27 (73.0)	36 (56.3)	0.135
PDA	15 (40.5)	19 (29.7)	0.283
PVL			0.383
-no	19 (51.4)	37 (57.8)	
-grade I	17 (45.9)	27 (42.2)	
-grade II	1 (2.7)	0	
IVH			0.410
-no	28 (75.7)	47 (73.4)	
-grade I/ II	9 (24.3)	13 (20.3)	
-grade III/IV	0	4 (6.3)	
Sepsis	21 (56.8)	41 (64.1)	0.527
NEC	4 (10.8)	5 (7.8)	0.721
Hyperbilirubinaemia	27 (73.0)	53 (82.8)	0.310
Hyperglycaemia	11 (29.7)	18 (28.2)	1.000
Hypoglycaemia	8 (21.6)	16 (25.0)	0.810
Hypothyroidism	2 (5.4)	2 (3.1)	0.622
NDO 2 year CA			0.376
-normal	30 (81.1)	45 (70.3)	
-mildly delayed	5 (13.5)	16 (25.0)	
-severely delayed	2 (5.4)	3 (4.7)	

SES: socio-economic status, Maternal educational level was available in 87.1%. GA: gestational age, SGA: small for gestational age < p10, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, NDO: neurodevelopmental outcome, Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2, CA: corrected age.

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7

Motor outcome over time of preterm born children ≤ 750g at birth

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Abstract

Background Extremely low birth weight (ELBW) infants are at risk of motor impairment and follow-up is therefore of major importance. However, the stability of motor developmental outcome in early childhood is questionable.

Aims To describe motor development at 2, 3.5 and 5.5 years in an ELBW cohort and to investigate the stability of motor development between these test ages.

Study design A retrospective cross-sectional and longitudinal cohort study. *Subjects* 100 preterm born children with a BW ≤750g, born between 1996-2005, who survived NICU admission and were included in a follow-up program.

Outcome measures Motor developmental outcome measured with three developmental tests depending on age of assessment, classified as normal (Z-score ≥-1), mildly delayed (-2 ≤ Z-score < -1) or severely delayed (Z-score < -2).

Results At 2, 3.5 and 5.5 years 60%, 74% and 42% had a normal motor developmental outcome. The stability of the motor outcome ranged from 46% to 53% between the test ages, and poor predictive values were found (C-statistics ranged between 0.57-0.63).

Conclusions A considerable number of ELBW children ≤750g had a delayed motor development at 2, 3.5 and especially at 5.5 years. Early classification of motor development did not correlate well with outcome at older ages, indicating that motor developmental impairment cannot be accurately identified in early infancy, stressing the importance of long-term follow-up.

Introduction

Despite advances in obstetric and neonatal care and improving survival, a considerable prevalence of cognitive impairment and motor dysfunction remains to be found in extremely preterm born and extremely low birth weight (ELBW) children.[1-11] The presence of developmental deficits are thought to be related to the modification of the normal pattern of development by disturbances of brain function caused both by interruption of normal brain maturation ex-utero and focal brain lesions, such as intraventricular hemorrhages (IVH) and periventricular leukomalacia (PVL) following very preterm birth.[12,13]

Motor dysfunction may interfere with the acquisition of everyday skills and cognitive and social-emotional development. Because of this effect on adaptive functioning, impaired motor development is a risk factor for later poor cognitive performance, learning disabilities and behavioural problems.[9,14,15]

In this study we focussed on motor developmental impairment in extremely preterm born and ELBW children. Motor impairment at 2 years corrected age (CA), defined as Psychomotor Developmental Index (PDI) < 70 on the Bayley Scales of Infant Development (BSID-II), has been reported to vary between 7.9% and 33.1%.[16-20] At early school-age (5 to 7 years of age) abnormal motor development, defined as Total Impairment Score (TIS) < p5 on the Movement Assessment Battery for Children (M-ABC), ranges from 19.2% to 30.7%.[8,10,21-23] Furthermore, severe impairment due to cerebral palsy (CP) is also common, with reported prevalence rates of CP among preterm born and ELBW children between 2% and 19%.[6,8,16,24-29]

Erikson et al. stated that serial motor assessments over time give the best indication of motor developmental outcome.[21] However, others have shown that the stability of motor developmental outcome of ELBW children in early childhood is questionable; the outcome either deteriorated or improved in comparison with school-age.[17,30,22,48]

Following our reports on survival, neonatal morbidity and neurodevelopmental outcome in infants with a birth weight (BW) ≤ 750g, we now present a retrospective cross-sectional and longitudinal cohort study on motor development of these ELBW children.[4,7] The objectives were to describe motor development at 2, 3.5 and 5.5 years of age to investigate the stability of the motor developmental classification between these test ages, and to determine if early prediction was possible. Furthermore, a comparison between appropriate and small for gestational age (AGA) and (SGA) children was made and right and left-handed children were compared.

Materials and methods

Subjects

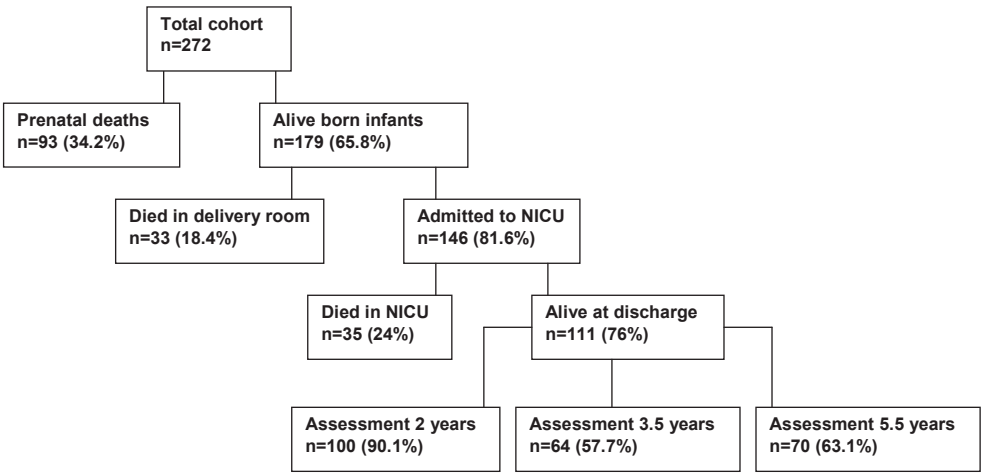
The original study population consisted of a cohort of 272 infants with a BW ≤ 750g and a gestational age (GA) of ≥ 24 completed weeks, born between 01-01-1996 and 31-12-2005.

Intra-uterine death occurred in 93 (34.2%) infants and 179 (65.8%) infants were born

alive of whom 33 died in the delivery room and 146 infants were admitted to the level three Neonatal Intensive Care Unit (NICU) of the Wilhelmina Children's Hospital, University Medical Centre Utrecht in the Netherlands. Thirty-five infants (24%) died in the NICU. Of the 111 survivors, 100 children (90.1%) were assessed at 2 years CA, 64 (57.7%) at 3.5 years and 70 (63.1%) at 5.5 years of age (Figure 1).
Furthermore, 63 children were assessed at both 2 and 3.5 years, 69 at 2 and 5 years, 50 at 3.5 and 5.5 years and 48 children at 2, 3.5 and 5.5 years of age. The 100 children assessed at 2 years CA form the basis of the analyses presented in this manuscript.

Details of ethics approval
All patients admitted to our University Medical Centre do give consent for the use of patient data for scientific research in which their data are processed anonymously. The parents of the study subjects agreed to participate in the neonatal follow-up program of the Wilhelmina Children's Hospital, and gave consent for using these data for scientific research in which their data are processed anonymously.

Figure 1. Follow-up of the study population with a birth weight ≤ 750g born between 1996-2005.



Data collection and definitions
Data were collected by reviewing the medical charts. GA was based on the last menstrual period and early ultrasound examination. GA categories were classified per week. For example, the category 24 weeks includes a GA of 24 weeks and 0 days till 24 weeks and 6 days. BW percentiles were determined according to the Dutch Perinatal Registry.[31,32] SGA was defined as a BW below the 10th centile.
Parental educational levels were recorded according to the occupational classification

standard of Statistics Netherlands.[33] Socio-economic status (SES) was recorded according to the zip code estimated income of The Netherlands Institute for Social Research.[34] Neonatal morbidity and interventions during NICU admission were described in our previous reports.[3,7] The gross motor function of children with CP was classified according to the gross motor function classification system.[35] Walking attainment was recorded in months CA.

The assessment at 2 years CA consisted of either the Griffiths Mental Developmental Scales (GMDS, n=49) or the Bayley Scales of Infant Development-second edition-Dutch version (BSID-II-NL, n=51), performed by certified investigators. The GMDS was used in the majority of the children between 1996 and 2000, and since December 2000 onwards the BSID-II-NL was used in our hospital. The GMDS consists of five subscales: locomotor, personal-social, hearing-language, eye-hand coordination and performance. This test is designed to yield both global (sum of five subscales) and subscale developmental quotients (DQ) with a mean (±SD) DQ score for the general population of 100 (±12).[36,37] Assessment of motor development with the GMDS in our study was based on the subscales locomotor (LM) and eye-hand coordination (EH). The BSID-II-NL consists of a Mental Scale and a Psychomotor Scale. For the assessment of motor development the Psychomotor Developmental Index (PDI) was used, with a mean of 100 (±SD 15).[38] In case of a PDI <55, 54 was entered in the dataset.

At 3.5 years of age the GMDS was used, and again motor development was based on the subscales LM and EH. At 3.5 years of age the mean (±SD) DQ score for the general population is 100 (±15).[37]

At 5.5 years of age handedness was inquired and motor development was assessed by means of the Movement Assessment Battery for Children (M-ABC). In the majority of our study population the first version of the M-ABC (n=50) was used, however in 2007 a new version became available and from October 2007 onwards the children in our follow-up program were assessed with the second version: M-ABC-2 (n=20). The M-ABC assesses manual dexterity, ball skills and static and dynamic balance by 8 motor tasks. Performance scores are calculated for each subscale, as well as for a total impairment score (TIS). With the M-ABC-2, manual dexterity, aiming and catching and balance by 8 motor tasks are assessed and scores are calculated for each subscale, as well as for a total test score (TTS). The motor abilities assessed with both the M-ABC and M-ABC-2 are similar. The total and subscale test scores of the M-ABC and M-ABC-2 are interpreted as normal (score > p15), at risk (p6 to p15) or abnormal (≤ p5).[39-41]

Motor developmental scores at 2 years of age were calculated for CA. Motor developmental scores at 3.5 and 5.5 years of age were no longer corrected for age (uncorrected age, UCA). Z-scores were calculated for all motor developmental scores in order to compare the motor outcome at 2, 3.5 and 5.5 years of age. Motor outcome was classified as normal (Z-score ≥-1), mildly delayed (-2 ≤ Z-score < -1) or severely delayed (Z-score < -2).

Statistical analysis

To check for accuracy, data entered were double checked. All analyses were performed using SPSS (version 15.0) software (SPSS Inc., Chicago, IL, USA). For statistical comparisons of continuous variables, the Mann-Whitney test was used. A Chi-square test or Fisher's exact test was used in case of dichotomous and categorical variables. A *p* value <0.05 was considered to be statistically significant.

Comparisons of motor developmental outcome at 2, 3.5 and 5.5 years of age were expressed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Furthermore, to examine the predictive value of the classification of motor development between the three test ages, the C-statistic for discrimination was derived from Somer's D. A C-Statistic of 0.6 to 0.7 is generally considered to be of limited value, 0.7 to 0.8 has modest value, and values > 0.8 are considered to have adequate discrimination for genuine clinical utility.[41]

Various subjects had missing values for motor developmental outcome at 3.5 and 5.5 years of age. Exclusion of the subjects with missing values, yields biased results as children who are lost to follow-up are often selectively missing, which also seemed to be the case in our study (Table 7). Hence, we imputed missing values by single imputation.[43,44]

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 100 children who have been assessed at 2 years CA. The median BW was 673g and median GA was 28 weeks. SGA infants had a significantly lower BW than AGA infants (635g versus 710g, *p*<0.001), whereas a significantly shorter GA was found in AGA infants (26.7 versus 28.8 weeks, *p*<0.001). All SGA infants were delivered by caesarean section compared to 59.1% of the AGA infants (*p*<0.001).

Motor developmental outcome at 2 years CA

Two children were diagnosed to have spastic bilateral CP, one SGA boy with PVL grade I and a large IVH (grade III according to Papile).The second was an AGA boy with asymmetrical dilatation of the lateral ventricles and PVL grade I but without evidence of IVH on cUS.[3,7]

The mean age of walking attainment was 16.3 months CA (range 9 to 23.5 months), and did not differ between AGA and SGA children (16.2 and 16.5 months CA, *p*= 0.801, Appendix Table 3).

Motor developmental outcome at 2 years CA of 100 children is presented in Table 2 and 3. The mean age at testing was 23 months (SD 2). These children were assessed by means of either the GMDS (n=49) or the BSID-II-NL (n=51). The children assessed with the GMDS performed significantly better compared to the

Table 1. Characteristics of 100 children with a birth weight ≤ 750g.

	Total cohort n=100	AGA n=44	SGA n=56	AGA vs SGA
	n	n (%)	n (%)	p-value
Median maternal age (years) (min-max)	30.0 (17-45)	29.5 (19-43)	31.0 (17-45)	0.191
Median birth weight (gram) (min-max)	673 (480-750)	710 (580-750)	635 (480-750)	**<0.001**
Median gestational age (weeks) (min-max)	28.00 (24.84-34.42)	26.77 (24.84-29.42)	28.84 (26.28-34.42)	**<0.001**
Multiple birth	20	13 (29.5)	7 (12.5)	**0.045**
Male	44	14 (31.8)	30 (53.6)	**0.042**
Caucasian ethnicity	92	39 (88.6)	53 (94.6)	0.295
SES				0.404
-high	20	8 (18.6)	12 (21.4)	
-average	64	26 (60.5)	38 (67.9)	
-low	15	9 (20.9)	6 (10.7)	
Maternal educational level				0.308
-high	12	5 (15.6)	7 (20.0)	
-average	28	11 (34.4)	17 (48.6)	
-low	27	16 (50.0)	11 (31.4)	
Prenatal steroids (GA <32 weeks)	80	38 (86.4)	42 (85.7)	1.000
Caesarean delivery	82	26 (59.1)	56 (100)	**<0.001**
5-min Apgar score <7	12	8 (18.2)	4 (7.1)	0.124

Total cohort: children born in 1996-2005, GA: gestational age, AGA: appropriate for gestational age: birth weight (BW) ≥p10, SGA: small for gestational age BW <p10. SES: socio-economic status, maternal educational level was available in 87.1%.

children who were assessed with the BSID-II-NL (p <0.001, Table 2). However, the distribution of the GMDS and BSID-II-NL assessments was not significantly different between AGA (GMDS n=23, BSID-II-NL n=21) and SGA (GMDS n=26, BSID-II-NL n=30) children (p= 0.687).

Sixty percent of the children had a normal motor developmental outcome, 28% a mildly delayed and 12% a severely delayed outcome. A normal motor developmental outcome was significantly more often found in AGA children (75.0% versus 48.2% in SGA, p= 0.008).

Motor developmental outcome at 3.5 years of age

Motor developmental outcome at 3.5 years of age is presented in Table 3. These children were all assessed by means of the GMDS. The mean age at testing was 41.4 months (SD 2.9): 74% of the children had a normal motor developmental outcome, 23% a mildly delayed and 3% a severely delayed outcome. No significant differences were noted between AGA and SGA children.

Motor developmental outcome at 5.5 years of age

The results of the M-ABC at 5.5 years of age are shown in Table 3. The mean age at testing was 5.6 years (SD 0.8). Less than half (42%) of the children had a normal motor developmental outcome, 28% a mildly delayed and 30% a severely delayed outcome. No significant differences were noted between AGA and SGA children.

The subscale test scores for manual dexterity, ball skills/ aiming and catching and static and dynamic balance have been analysed in the 70 children in whom the M-ABC and M-ABC-2 was performed. The children especially showed a poor performance on the balance test (48.6% normal, whereas respectively 64.3% and 55.7% of the children were classified as normal for manual dexterity and ball skills/ aiming and catching respectively, Table 6.).

Table 2. Motor developmental outcome at 2 years CA assessed with the GMDS or BSID-II-NL.

	Total cohort n=100	GMDS n=49	BSID-II-NL n=51	GMDS vs BSID-II-NL p-value
Mean Z-score	-0.82	-0.41	-1.18	**<0.001**
(SD, min~max)	(0.9, -2.73~1.62)	(1.0, -3.10~1.73)	(0.8, -2.73~1.13)	
Normal, n (%)	60	42 (85.7)	18 (35.3)	**<0.001**
Mildly delayed, n (%)	28	5 (10.2)	23 (45.1)	
Severely delayed, n (%)	12	2 (4.1)	10 (19.6)	

GMDS: Griffiths Mental Development Scales, subscale locomotor + subscale eye-hand coordination, BSID-II-NL: Bayley Scales of Infant Development-II-Dutch version, mental scale. Total cohort: combined GMDS and BSID-II-NL assessments. SD: standard deviation, min: minimum, max: maximum. Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.

Motor developmental outcome over time

An overview of the motor developmental outcome over time is presented in Figure 2. In summary, a normal motor developmental outcome was achieved in 60%, 74% and 42% at 2, 3.5 and 5.5 years of age respectively.

Comparison of outcome at 2 and 3.5 years of age

Of the children with a normal motor developmental outcome at 2 years CA, 47/60 (78.3%) also had a normal outcome at 3.5 years of age, whereas 12/60 (20%) deteriorated to a mildly delayed motor developmental outcome.

Of the children who were mildly delayed at 2 years CA, 5/28 (17.9%) remained mildly delayed at 3.5 years, 22/28 (78.6%) improved to a normal motor developmental outcome and 1/ 28 (3.6%) deteriorated to the severely delayed category.

As for the 12 severely delayed children at 2 years CA, 6 children improved to a mildly delayed category at 3.5 years of age and 5 to a normal motor developmental outcome.

Table 3. Motor developmental outcome at 2, 3.5 and 5.5 years of age.

	Total cohort n=100	AGA n=44	SGA n=56	AGA vs SGA p-value
2 years CA				
Mean Z-score	-0.82	-0.59	-1.00	**0.016**
(SD, min~max)	(0.9, -2.73~1.62)	(0.9, -2.73~1.62)	(0.8, -2.49~0.98)	
Normal, n (%)	60	33 (75.0)	27 (48.2)	**0.021**
Mildly delayed, n (%)	28	7 (15.9)	21 (37.5)	
Severely delayed, n (%)	12	4 (9.1)	8 (14.3)	
3.5 years UCA				
Mean Z-score	-0.75	-0.73	-0.76	0.610
(SD, min~max)	(0.6, -2.83~1.30)	(0.6, -2.49~0.44)	(0.6, -2.83~1.30)	
Normal, n (%)	74	33 (75.0)	41 (73.2)	0.717
Mildly delayed, n (%)	23	9 (20.5)	14 (25.0)	
Severely delayed, n (%)	3	2 (4.5)	1 (1.8)	
5.5 years UCA				
Mean Z-score	-1.49	-1.25	-1.67	0.134
(SD, min~max)	(1.6, -6.15~0.93)	(1.5, -5.25~0.90)	(1.6, -6.15~0.93)	
Normal, n (%)	42	22 (50.0)	20 (35.7)	0.363
Mildly delayed, n (%)	28	11 (25.0)	17 (30.4)	
Severely delayed, n (%)	30	11 (25.0)	19 (33.9)	

Total cohort: children born in 1996-2005, AGA: appropriate for gestational age birth weight (BW) ≥p10, SGA: small for gestational age BW <p10. Motor outcome: at 2 year: Griffiths Mental Development Scales (GMDS), subscale locomotor (LM) + subscale eye-hand coordination (EH) or Bayley Scales of Infant Development-II, motor scale. 3.5 year: GMDS LM + EH. 5.5 year: Movement-ABC Total Impairment Score. CA: corrected age, UCA: uncorrected age, Outcome: normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2. For missing values of motor outcome at 3.5 and 5.5 years single imputation was used.

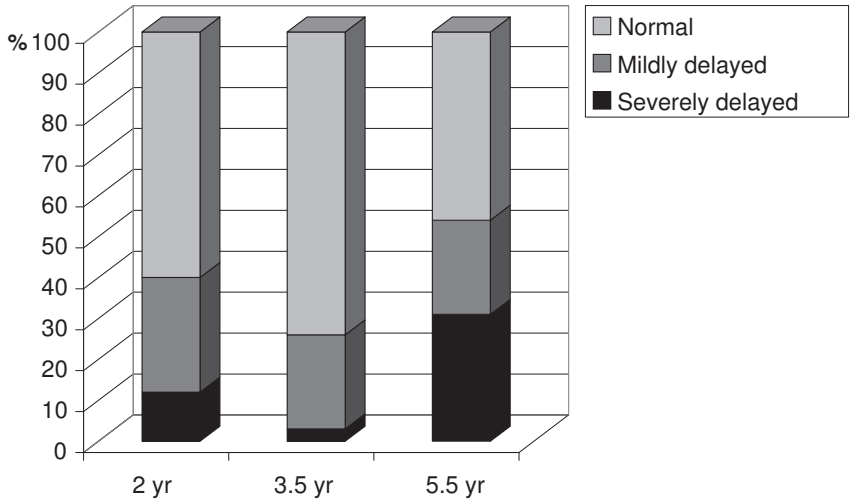
So, altogether 53/100 children (53%) remained in the same category at 2 and 3.5 years of age. The C-statistic of 0.57 showed a moderate predictive value of motor developmental outcome at 2 years CA for the outcome at 3.5 years of age (Table 4a). The sensitivity for normal outcome at both 2 and 3.5 years was 63.5% with a PPV of 78.3%, and the specificity for abnormal outcome (mildly and severely delayed) at both ages was 50% with a NPV of 32.5% (Table 5).

Comparison of outcome at 2 and 5.5 years of age

Of the children with a normal motor developmental outcome at 2 years CA 29/60 (48.3%) also had a normal outcome at 5.5 years, 16/60 (26.7%) deteriorated to a mildly delayed outcome and 15/60 (25%) to a severely delayed category.

Of those with a mildly delayed outcome at 2 years CA, 9/28 (32.1%) remained in the same category at 5.5 years of age, whereas 12/28 (42.9%) improved to a normal

Figure 2. Overview of motor developmental outcome over time of 100 children ≤ 750g.



2 yr CA: GMDS LM + EH or BSID-II-NL motor scale, 3.5 yr: GMDS LM + EH, 5.5 yr: M-ABC Total Impairment Score. Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2

outcome and 7/28 (25.0%) deteriorated to a severely delayed outcome. Of the 12 severely delayed children at 2 years CA, 8 children remained severely delayed, 3 improved to a mildly delayed category and 1 improved to a normal outcome at 5.5 years of age. So, only 46/100 children (46%) remained in the same category at 2 and 5.5 years of age. The C-statistic of 0.61 showed a moderate predictive value of motor developmental outcome at 2 years CA for the outcome at 5.5 years of age (Table 4b). The sensitivity and PPV for normal outcome was 69.0% and 48.3% respectively, and the specificity and NPV for abnormal outcome was 46.6% and 67.5% respectively (Table 5). Furthermore, the PDI showed a better predictive value for the outcome at 5.5 years of age than the LM and EH subscale scores of the GMDS (PPV of 66.7% and 40.5% respectively, Appendix Tables 4a, 4b and 5).

Comparison of outcome at 3.5 and 5.5 years of age

The motor developmental outcome at 3.5 and 5.5 years of age are shown in Table 4c: 35/74 (47.3%) children with a normal motor developmental outcome at 3.5 years also had a normal outcome at 5.5 years of age, 20/74 (27.0%) deteriorated to the mildly delayed category and 19/74 (25.7%) to the severely delayed one. Of the children with a mildly delayed motor developmental outcome at 3.5 years of age, 8/23 (34.8%) remained mildly delayed at 5.5 years of age, 8/23 (34.8%) children

Table 4a. Classification of motor developmental outcome at 2 and 3.5 years of age in 100 ELBW children.

Motor development classification at 2 y	Motor development classification at 3.5 y, n (%)			
	Normal	Mildly delayed	Severely delayed	Total, n (%)
Normal	47 (78.3) [a]	12 (20.0) [c]	1 (1.7) [c]	60 (60)
Mildly delayed	22 (78.6) [b]	5 (17.9) [a]	1 (3.6) [c]	28 (28.0)
Severely delayed	5 (41.7) [b]	6 (50.0) [b]	1 (8.3) [a]	12 (12.0)
Total, n (%)	74 (74.0)	23 (23.0)	3 (3.0)	100 (100)

Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.
Percentages are row percentages, except for the totals for 2 years, which are column percentages.
[a] unchanged, [b] improved, [c] deteriorated. For missing values of motor outcome at 3.5 of age single imputation was used. C-statistic = 0.573 95% CI [0.487-0.658].

Table 4b. Classification of motor developmental outcome at 2 and 5.5 years of age in 100 ELBW children.

Motor development classification at 2 y	Motor development classification at 5.5 y, n (%)			
	Normal	Mildly delayed	Severely delayed	Total, n (%)
Normal	29 (48.3) [a]	16 (26.7) [c]	15 (25.0) [c]	60 (60)
Mildly delayed	12 (42.9) [b]	9 (32.1) [a]	7 (25.0) [c]	28 (28)
Severely delayed	1 (8.3) [b]	3 (25.0) [b]	8 (66.7) [a]	12 (12)
Total, n (%)	42 (42.0)	28 (28.0)	30 (30.0)	100 (100)

Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.
Percentages are row percentages, except for the totals for 2 years, which are column percentages.
[a] unchanged, [b] improved, [c] deteriorated. For missing values of motor outcome at 5.5 years of age single imputation was used. C-statistic = 0.611 95% CI [0.517-0.705].

Table 4c. Classification of motor developmental outcome at 3.5 and 5.5 years of age in 100 ELBW children.

Motor development classification at 3.5 y	Motor development classification at 5.5 y, n (%)			
	Normal	Mildly delayed	Severely delayed	Total, n (%)
Normal	35 (47.3) [a]	20 (27.0) [c]	19 (25.7) [c]	74 (74.0)
Mildly delayed	7 (30.4) [b]	8 (34.8) [a]	8 (34.8) [c]	23 (23.0)
Severely delayed	0	0	3 (100) [a]	3 (3.0)
Total, n (%)	42 (42.0)	28 (28.0)	30 (30.0)	100 (100)

Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.
Percentages are row percentages, except for the totals for 3.5 years, which are column percentages.
[a] unchanged, [b] improved, [c] deteriorated. For missing values of motor outcome at 3.5 and 5.5 years of age single imputation was used. C-statistic = 0.627 95% CI [0.514-0.739].

deteriorated to the severely delayed category and 7/23 (30.4%) improved to normal. The 3 children with a severely delayed motor developmental outcome at 3.5 years of age remained severely delayed at 5.5 years of age. So, only 46/100 children (46%) remained in the same category at 3.5 and 5.5 years of age. The C-statistic of 0.63 showed a moderate predictive value of motor developmental outcome at 3.5 years for the outcome at 5.5 years of age (Table 4c). The sensitivity for normal outcome was 83.3% with a PPV of 47.3%, and the specificity for abnormal outcome at both ages was 32.8% with a NPV of 73.1% (Table 5).

Table 5. Predictive value of motor developmental outcome at 2, 3.5 and 5.5 years of age.

	Sensitivity	Specificity	PPV	NPV
	%	%	%	%
2 for 3.5 years	63.5	50.0	78.3	32.5
2 for 5.5 years	69.0	46.6	48.3	67.5
3.5 for 5.5 years	83.3	32.8	47.3	73.1

PPV: positive predictive value, NPV: negative predictive value.

Right-and left handedness and motor development

Of the 70 children who were assessed at 5.5 years of age, 53 children were right-handed (75.7%), 16 left-handed (22.9%) and 1 child (1.4%) was ambidexter.

A comparative analysis (Table 6) showed no significant differences in performance on the M-ABC between the right and left-handed children, although there was a non-significant trend in better performance (i.e. a higher percentage of normal scores) of right-handed children at all subscales.

Furthermore, the best performance was seen on manual dexterity (64.3% had a normal score) and the worst on balance (normal score in 48.6%).

The motor developmental assessments at 2 years CA and 3.5 years of age also showed no significant differences in outcome between right and left-handed children (Appendix Table 6).

Motor developmental outcome per GA

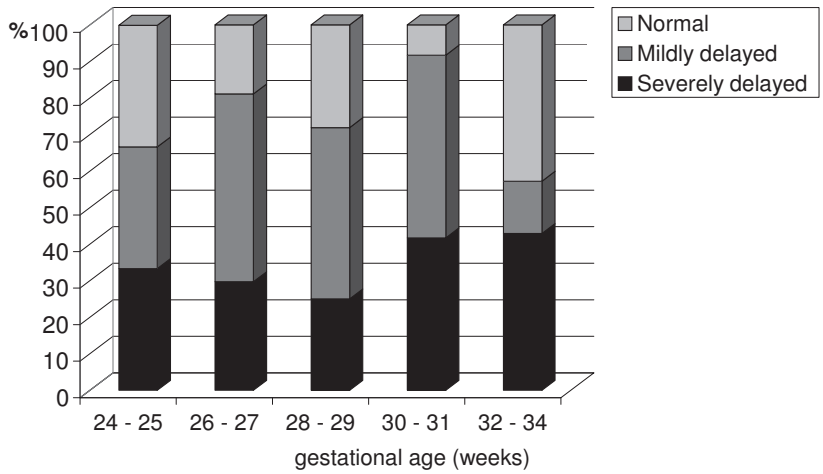
In Figure 3a, 3b and 3c, the results of the analysis of motor developmental outcome per GA subgroups are shown. Children with a mildly or severely delayed outcome are especially found in the upper GA categories, indicating a poorer outcome for extremely SGA children. It should however be noted that some GA subgroups are represented by small numbers of children.

Table 6. Motor developmental outcome at 5.5 years of age of right and left-handed ELBW children.

	Total n=70 n (%)	Right-handed n=53 n (%)	Left-handed n=16 n (%)	Ambidexter n=1 n (%)	Right vs left-handed p-value
TIS					
Normal	34 (48.6)	27 (50.9)	7 (43.8)	0	0.643
At risk	13 (18.6)	10 (18.9)	2 (12.5)	1 (100)	
Abnormal	23 (32.9)	16 (30.2)	7 (43.8)	0	
Manual dexterity					
Normal	45 (64.3)	35 (66.0)	9 (56.3)	1 (100)	0.594
At risk	14 (20.0)	11 (20.8)	3 (18.8)	0	
Abnormal	11 (15.7)	7 (13.2)	4 (25.0)	0	
Aiming & catching					
Normal	39 (55.7)	32 (60.4)	6 (37.5)	1 (100)	0.294
At risk	15 (21.4)	10 (18.9)	5 (31.3)	0	
Abnormal	16 (22.9)	11 (20.8)	5 (31.3)	0	
Balance					
Normal	34 (48.6)	29 (54.7)	5 (31.3)	0	0.194
At risk	16 (22.9)	10 (18.9)	6 (37.5)	0	
Abnormal	20 (28.6)	14 (26.4)	5 (31.3)	1 (100)	

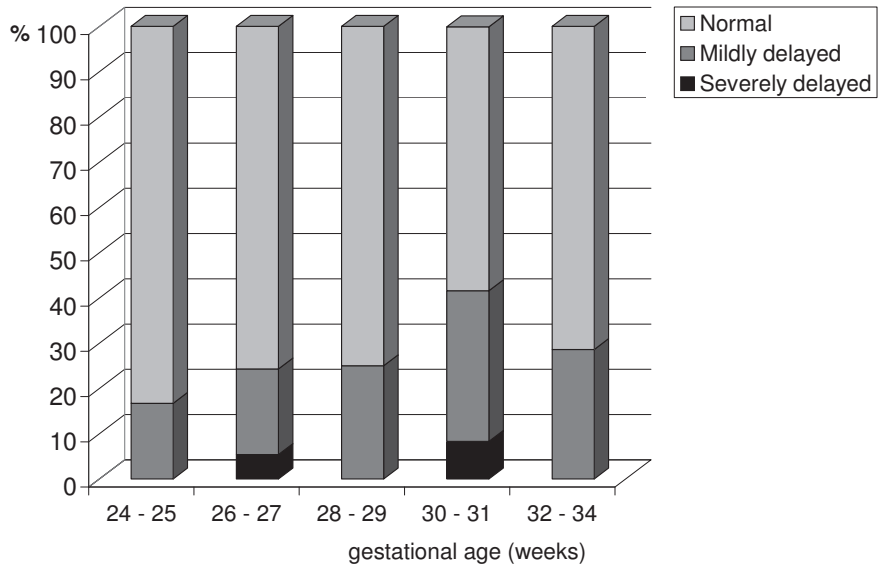
Motor developmental outcome at 5.5 years of age assessed with M-ABC. TIS: total impairment score. Normal: > p15, at risk: p6-P15, abnormal: ≤ p5. P-value indicates comparison of normal performance of right versus left-handed children.

Figure 3a. Motor developmental outcome at 2 years per GA (n=100).



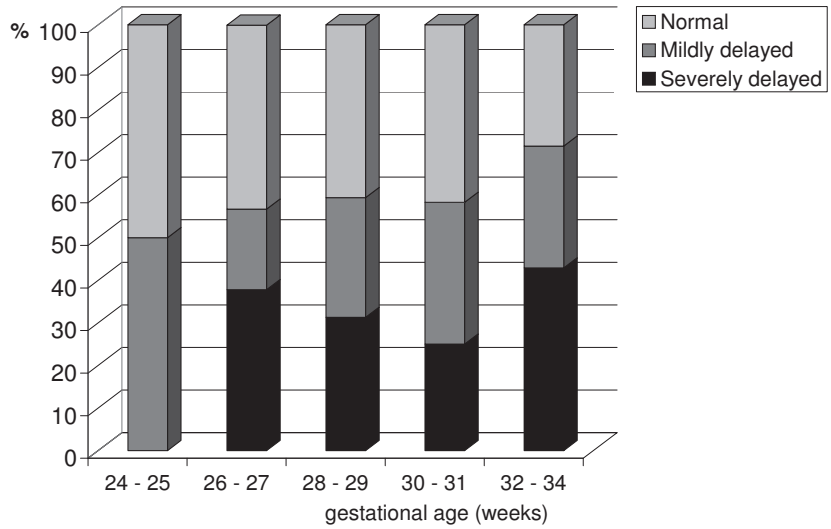
Motor development assessed with GMDS or BSID-II. 24-25: n=12, 26-27: n=37, 28-29: n=32, 30-31: n=12, 32-34: n=7. Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.

Figure 3b. Motor developmental outcome at 3.5 years per GA (n=100).



Motor development assessed with GMDS. 24-25: n=12, 26-27: n=37, 28-29: n=32, 30-31: n=12, 32-34: n=7. Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.

Figure 3c. Motor developmental outcome at 5.5 years per GA (n=100).



Motor development assessed with M-ABC. 24-25: n=12, 26-27: n=37, 28-29: n=32, 30-31: n=12, 32-34: n=7. Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.

Discussion

Results of this study indicate that ELBW children ≤ 750g are at considerable risk of motor developmental impairment. A substantial part of these children did not achieve a normal motor developmental outcome (40%, 26% and 58% respectively) at 2, 3.5 and 5.5 years of age. In contrast with the results of other reports we found no significant differences in motor development between males and females at all test ages.[11,26,30]

Motor developmental outcome at 2 years CA

Literature presenting the data of a normal motor developmental outcome at 2 years CA in extremely preterm born and ELBW children varies over a substantial range from 33% to 70%.[16-20] In the studies cited, the BSID-II was performed, except for Stoelhorst et al. who used the BSID-I and reported the highest percentage of a normal PDI (70%) in a preterm cohort (GA < 32 weeks, born in 1996-1997).
It is likely that the their data overestimated the PDI by the use of the BSID-I, as the MDI and PDI scores of the BSID-II are on average 12 and respectively 15 points lower.[38,45]
Comparing our data with the other studies cited above, we demonstrated a better performance of our ELBW population. Only the data of Maguire et al. showed a somewhat more promising result with a normal outcome in 66.2% of their cohort of preterm infants (GA < 32 weeks, born between 2002 and 2004).[19]

Motor developmental outcome at 3.5 years of age

There are no studies describing motor development of ELBW children at 3.5 years of age. However, the results of studies reporting a normal motor developmental outcome in low BW cohorts at 3 years of age ranged from 30% to 67%.[46-49] However, the highest percentage of 67% was obtained from an assessment of gross motor function by Goyen et al.[46] The more recent literature shows poorer motor developmental outcomes, most likely as a result of the decreasing GA of surviving infants. Compared to other reports, our ELBW cohort showed a higher percentage of normal motor developmental outcome at 3.5 years of age.

Motor development at 5.5 years of age

At 5.5 years of age the majority of the children had a mildly or severely delayed motor development. As supported by others we showed that very preterm and ELBW children have more difficulties in keeping their balance than performing manual dexterity tasks and ball skills.[11,50] A poor motor development at school-age is also reported by others; a normal TIS ranged from 45% to 64%.[8,9,21,22,30] The highest percentage of normal motor development (64%) was found in a VLBW cohort studied by Erikson et al.[21] As for the other studies cited, their mean GA was considerably higher compared to our ELBW cohort, which may partially explain their better motor performance results.[8,9,21,22,30]

Motor development over time

Classification of motor development at 2 years CA differed considerable from the classification at 3.5 and 5.5 years of age. The stability of the motor developmental outcome ranged from 46% to 53% between the test ages, and therefore a poor to moderate sensitivity, specificity, PPV and NPV, as well as C-statistics of limited value were found.

The majority of the children who were classified as mildly or severely delayed at 2 years CA improved to normal at 3.5 years of age. However, a substantial percentage of the children classified as normal and mildly delayed at 3.5 years deteriorated to the severely delayed category at 5.5 years of age. In contrary, the majority of the children classified as severely delayed at 2 years CA and 3.5 years of age remained in this category at 5.5 years of age. The better performance of our ELBW cohort at 3.5 years is most likely due to the use of the GMDS, which is not a test meant for assessing motor performance[36,37] resulting in a high percentage of children with improving outcome in comparison with 2 years CA, and also a greater proportion of children who deteriorated to a poorer outcome at 5.5 years of age. In contrast to the M-ABC, the revised M-ABC-2 can already be used at the age of three years, which will hopefully make it possible to test motor outcome more reliably from an earlier age onward in future longitudinal cohort studies.

Our findings are partly comparable to those of Erikson et al. who reported that only 53.3% of their VLBW cohort displayed a stable motor development through all test ages (Movement Assessment of Infants at 5,10,18 months CA and M-ABC at 5.5 years). Of the children who showed unstable motor behaviour; 35.1% improved, 29.9% deteriorated and 35.1% fluctuated between the first and the last assessment.[21] In our study, the number of ELBW children with a normal motor developmental outcome at 5.5 years of age is smaller compared to the previous test ages.

Others reported that the prevalence of normal motor developmental outcome remained stable, decreased or increased over time.[17,46,48,30] A stable normal motor developmental outcome (71% and 70% at 18 and 24 months CA) was found by Stoelhorst et al. However, changes in PDI scores existed in 34%: of which half of the children had a worse psychomotor outcome and half had a better outcome at 24 months CA.[17] Although, it is likely that a six months difference between two assessments is not long enough to measure real changes in motor performance. In agreement with our results, Goyen et al. also showed that the percentage of children with normal gross and fine motor function significantly declined between 3 and 5 years of age (67% to 19% and 53% to 36% respectively).[46] On the contrary, Janssen et al. found an increased number of preterm born children (GA ≤ 32 weeks) with a normal motor outcome at 5 years compared to 2.5 years of age (71% and 55% respectively). However, a poor correlation between the PDI and TIS was shown (only 45% had both a normal outcome at 2.5 years and 5 years of age, rs=0.26).[30]

Differences in motor developmental outcome in early infancy and at school-age

might partially be explained by the following: understandably testing can be affected by a lack of concentration, tiredness, lack of cooperation, shyness and even fear. Not surprisingly, therefore, results obtained in early childhood are not necessarily identical when the same children are assessed in later life.[21,51] Sommerfelt et al. reported that motor behaviour in children may also partly depend on social factors, parental SES and educational levels.[51] Furthermore, the overlap of motor difficulties with attention, cognition and behavioural problems complicates measurement of motor function. Standardized motor tests require the subject to understand the test, maintain concentration on the task and to inhibit other distracters, in addition to having the necessary motor and visuospatial skills. Consequently, poor motor performance can occur for a variety of reasons.[14,21,51,52]

Influence of GA on motor development

A mildly or severely delayed outcome at 2 years CA and 5.5 years of age is especially common in the ELBW children born at the upper GA subgroups, indicating a poorer motor developmental outcome for extremely SGA children. The most plausible explanation is that brain development was adversely affected in these severely intra-uterine growth retarded ELBW children. Interesting is that the significantly poorer motor development of SGA children noted at 2 years CA was no longer seen at 3.5 and 5.5 years of age. The use of two developmental tests with different tasks at 2 years CA may have affected these results.[36-38] However, a comparison of the number of GMDS and BSID-II-NL assessments among the AGA and SGA children did not differ. We assume that brain plasticity as suggested by Luciana et al. can be a possible explanation for this finding.[53]

Furthermore, motor outcome can be influenced by height and weight. However, we found no important differences in the number of children with a height and weight below the 10th centile at 2 and 3.5 years of age (height < p10 in 59% and 64%, weight < p10 in 69% and 70% respectively, Appendix Table 7a and 7b).

Motor development and handedness

Our study failed to demonstrate a significant difference in motor development of right-handed compared to left-handed ELBW children, although we did show a trend of higher percentages of normal M-ABC scores in right-handed children.

Our findings are comparable Ross et al. who also found no significant differences in neurological status between left- and right-handed children.[54] However, Powls et al. reported impaired manual dexterity to be significantly more common in VLBW non-right handers.[55] The proportion of children with non-right lateralization is high in preterm born children. This non-right lateralization may represent poor neurological organization as a result of poor postnatal brain growth.[54,55] Bishop et al. even argues that neurological damage not only changes hand preference from right to left but that it also results in clumsiness of the right hand.[56] Another explanation might be the

higher prevalence of neonatal brain damage in preterm infants in the left hemisphere leading to impaired usage of the right hand.[57]

To appreciate the presented results, some issues need to be addressed. A limitation of this study is that we used four different instruments: at 2 years CA the GMDS or the BSID-II-NL, at 3.5 years of age the GMDS, and at 5.5 years of age the M-ABC or M-ABC-2. Advances in developmental assessments resulted in the use of two different tests at 2 years CA and two versions of the M-ABC were used. However, these problems will continue to exist as the BSID-III has now been introduced.
There are differences in standardization, theoretical construct and the demands on motor performance capacities between the used instruments. In order to make an accurate comparison between the motor assessments at different ages we therefore converted all test scores into Z-scores.
However, one should also take into account that the GDMS is not a test meant for assessing motor performance, while the M-ABC is. One can therefore argue whether one can really compare these two tests when assessing motor development.
Furthermore, the available norms of the GMDS are rather out-dated, which may have resulted in an overestimation of the motor developmental outcome of our cohort.[36,37]
In our study the motor developmental assessments at the ages of 2, 3.5 and 5.5 years took place during regular follow-up visits. However, as can be seen from Figure 1, not all children did undergo the assessment at each of the time points. We speculate about potential reasons for loss to follow-up in this cohort. One reason might be that the children were doing well and hence the parents did not feel the need for a visit to the follow-up clinic. Another reason might be that children were having problems and an intervention program was already initiated by the local pediatrician.
Altogether, at 2 years CA we were able to see 100/111 children (90.1%) for follow-up. The 11 children lost to follow-up before this time point up all survived till 2 years of age, were all Caucasian singletons of whom 5/11 (45.5%) were male and 8/11 (72.7%) SGA. Their neonatal morbidity was comparable to the children who were available for follow-up. The major reason for being lost to follow-up was the preference to visit the local pediatrician. We have no reason to suspect that these 11 children would have significantly altered our motor developmental outcome results.
At 3.5 years of age we were able to see 63 out of the 100 children (63%). Data on motor development of 37 children were missing; for three of them the GMDS could not be completed due to lack of cooperation. Of the remaining 18/34 children, the GMDS was not used by one of our neonatologists due to unfamiliarity with the test. However, his notes described a normal development in these 18 children. Unfortunately, 16 children were lost to follow-up at 3.5 years of age because of the above mentioned reasons.
We compared the baseline characteristics, neonatal complications and motor developmental outcome at 2 years CA between the non-missing and missing children

(Table 7). Children who were lost to follow-up had a lower BW, bronchopulmonary dysplasia (BPD) was more common and mechanical ventilation was required more often, but they had a significantly better motor developmental outcome at 2 years CA. Therefore, the motor development at 3.5 years of age based on 63 children might be biased and underestimated due to the lost to follow-up of children who were doing well at 2 years CA or overestimated due to the influence of a lower BW and a higher prevalence of BPD on development.[1-3,58] Hence, we decided to perform a single imputation missing value analysis. As a sensitivity analysis we compared these results with the results of the 63 children and found no major differences (normal motor development in 74% and 79.4% respectively).
At 5.5 years of age the M-ABC had been performed in 70 children. At present, 9 children are not yet 5.5 years of age. As motor developmental outcome might be influenced by handedness, we inquired all parents for handedness of their child. We succeeded to obtain this information for 87/100 (87%) children. We detected that the percentage of left-handed children was not significantly different between the 70 children in whom the motor assessment at 5.5 years of age had taken place and the 17 without M-ABC data (22.9% versus 23.5% respectively, p= 1.000). The missing value analysis, as described above was also performed for the motor developmental outcome results at 5.5 years of age.

Conclusion

In conclusion, ELBW children ≤ 750g are at considerable risk of motor developmental impairment at early infancy, especially at school-age. Classification of motor development at 2 years CA substantially differed from the classification at 3.5 and 5.5 years of age. Our data do suggest that 2 years CA is too early for diagnosing children with a delayed motor development, neither is it possible to reliably determine ELBW children with a normal motor development in early infancy. Long-term follow-up of these ELBW infants is therefore not only important for cognitive outcome but also for motor outcome.

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Table 7. Characteristics of missing versus non-missing motor outcome data at 3.5 years of age.

	Missing n=37	Non-missing n=63	Missing vs non-missing
	n (%)	n (%)	p-value
Median maternal age (years) (min-max)	29 (19-43)	31 (17-45)	0.490
Median birth weight (gram) (min-max)	640 (480-750)	690 (530-750)	**0.005**
Median gestational age (weeks) (min-max)	27.7 (25.0-34.4)	28.0 (24.8-32.8)	0.313
Multiple birth	8 (21.6)	12 (19.0)	0.799
Male	14 (37.8)	30 (47.6)	0.406
Ethnicity (Caucasian)	34 (91.9)	58 (92.1)	1.000
SES			1.000
-high	7 (18.9)	13 (21.0)	
-average	24 (64.9)	40 (64.5)	
-low	6 (16.2)	9 (14.5)	
Maternal educational level			0.208
-high	2 (7.4)	10 (25.0)	
-average	13 (48.1)	15 (37.5)	
-low	12 (44.4)	15 (37.5)	
Prenatal steroids (GA <32 wks)	29 (87.9)	51 (85.0)	0.766
Caesarean delivery	30 (81.1)	55 (82.5)	1.000
5-min Apgar score <7	5 (13.5)	7 (11.1)	0.756
SGA	19 (51.4)	37 (58.7)	0.534
NICU admission > 28 days	33 (89.2)	53 (84.1)	0.563
Mechanical ventilation			**0.016**
-no	4 (10.8)	16 (25.4)	
-short < 2 weeks	7 (18.9)	22 (34.9)	
-intermediate	16 (43.2)	19 (30.2)	
-long	10 (27.0)	6 (9.5)	
Oxygen	36 (97.3)	55 (87.3)	0.148
IRDS			0.409
-no	13 (35.1)	29 (46.0)	
-grade I/II	10 (27.1)	18 (28.6)	
-grade III/ IV	14 (37.8)	16 (25.4)	
BPD	27 (73.0)	30 (47.6)	**0.021**
Sepsis	21 (56.8)	40 (63.5)	0.531
Hypotension	27 (73.0)	36 (57.1)	0.136
PVL			0.238
-no	18 (48.6)	38 (60.3)	
-grade I	18 (48.6)	25 (39.7)	
-grade II	1 (2.7)	0	

	Missing n=37 n (%)	Non-missing n=63 n (%)	Missing vs non-missing p-value
IVH			0.441
-no	29 (78.4)	45 (71.4)	
-grade I/ II	8 (21.6)	14 (22.2)	
-grade III/IV	0	4 (6.3)	
Hyperbilirubinaemia	27 (73.0)	52 (82.5)	0.312
Hyperglycaemia	11 (29.7)	18 (28.6)	1.000
Hypoglycaemia	9 (24.3)	15 (23.8)	1.000
Hypothyroidism	2 (5.4)	2 (3.2)	0.625
NEC	4 (10.8)	5 (7.9)	0.722
PDA	14 (37.8)	19 (30.2)	0.510
Motor development 2 year CA			**0.007**
-normal	29 (78.4)	31 (49.2)	
-mildly delayed	4 (10.8)	24 (38.1)	
-severely delayed	4 (10.8)	8 (12.7)	

SES: socio-economic status. GA: gestational age, SGA: small for gestational age: birth weight < p10, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, Motor development: normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2, CA: corrected age.

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8

Postnatal growth of preterm born children ≤ 750 gram at birth

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Abstract

Background Extremely low birth weight (ELBW) infants are at risk of impaired postnatal growth. Postnatal catch-up and catch down growth have been reported to be associated with cognitive and motor development.

Objectives To describe postnatal growth patterns of appropriate and small for gestational age (AGA and SGA) ELBW children in relation to their cognitive and motor outcome at 5.5 years.

Study design A retrospective cohort study of 101 children with a BW ≤750g, born between 1996-2005.

Results Between birth and 5.5 years of age catch-up growth in height (Ht), weight for height (Wt/Ht), weight (Wt) and occipital-frontal circumference (OFC) was seen in 72.7%, 79.5%, 56.8% and 44.1% respectively of the SGA children. Catch-up mostly occurred between birth and 2 years CA. For AGA children we found substantial catch-down growth for Ht (15.4%), Wt (30.8%) and OFC (18.2%). Cognitive and motor outcome was normal in 76.2% and 41.6% of AGA and SGA children. While cognitive outcome did not differ between the children with different growth patterns, significantly more SGA children without catch-up growth in Wt/Ht had a severely delayed motor outcome compared to SGA children with catch-up (55.6% vs 22.9%, p=0.008). Also, significantly more AGA children with catch-down growth in OFC had a severely delayed motor outcome compared to AGA children with adequate growth (66.7% vs 11.1%, p=0.015).

Conclusions Catch-up growth for Ht and Wt/Ht occurred in the majority of the SGA children with a BW ≤ 750g, but was less common for Wt and OFC. ELBW AGA children display catch-down growth especially in Wt and OFC. Lack of catch-up growth in Wt/Ht and catch-down growth in OFC are associated with the poorest motor outcome. Cognitive outcome was not significantly associated with the different growth patterns.

Introduction

It is well known that extremely preterm born infants and extremely low birth weight (ELBW) infants are at increased risk of cognitive and motor impairment as well as growth failure.[1-18]

In many studies these children are classified as appropriate for gestational age (AGA) or small for gestational age (SGA). However, the definition used for SGA differs in the literature. Among paediatric endocrinologists there is consensus that a birth weight (BW) and/ or length <-2 standard deviation scores (SDS) should be the cut off-value.[19,20] Neonatologists tend to use the 5th or 10th percentiles for gestational age (GA) of the various growth parameters, since these cut-offs have been shown to be related to later development.[11,15,21,22]

SGA children have been reported to show catch-up growth, mostly during the first 2 years of life. However, the percentage of catch-up growth in height of preterm ELBW and VLBW SGA children is different in various studies ranging from 55% to 92%.[10,15,16,23-25] AGA children may display catch-down growth, percentages varying from 2% to 28.9%.[15,23,25]

Postnatal growth failure has been reported to be associated with an increased risk of poor cognitive and motor developmental outcome.[12,13,15-18] Poor growth, particularly of the head, as well as of height (Ht) and weight (Wt), has been associated with poorer cognitive and motor outcomes at school age in a number of studies [15,16, 18,26-32] Some studies found that neurodevelopmental impairments are especially common in SGA children.[11,33-35] However, others showed that the course of postnatal growth rather than the appropriateness of Wt for GA at birth seems to predict later neurodevelopmental outcome in preterm children with very low birth weight.[15,26]

Improvements in neonatal care have resulted in an increased survival of ELBW infants born at decreasing birth weights and gestational ages. The fact that these children still remain at increased risk of developmental impairments illustrates the importance of follow-up studies.[1-18] To the best of our knowledge, studies describing the growth pattern of ELWB children with a BW ≤750g have not been reported. Therefore, following our reports on survival, neonatal morbidity and developmental outcome of ELBW children with a BW ≤750g, we now present a retrospective cohort study on postnatal growth of these ELBW children.[9,36-38] The objectives were to describe growth (height (Ht), weight (Wt) and occipital-frontal circumference (OFC)) at birth, 15 months corrected age (CA), 2 years CA, 3.5 and 5.5 years of age.

AGA children (Ht or Wt at birth ≥-2 SDS) were compared with SGA children (Ht and/or Wt at birth <-2 SDS). For growth in OFC a separate comparison was made between AGA (OFC at birth ≥p10) and SGA (OFC at birth <p10) children.

For all growth parameters the occurrence of catch-up and catch-down growth was examined. Furthermore, this study aimed to examine the association between postnatal growth patterns and cognitive and motor developmental outcome at 5.5 years of age.

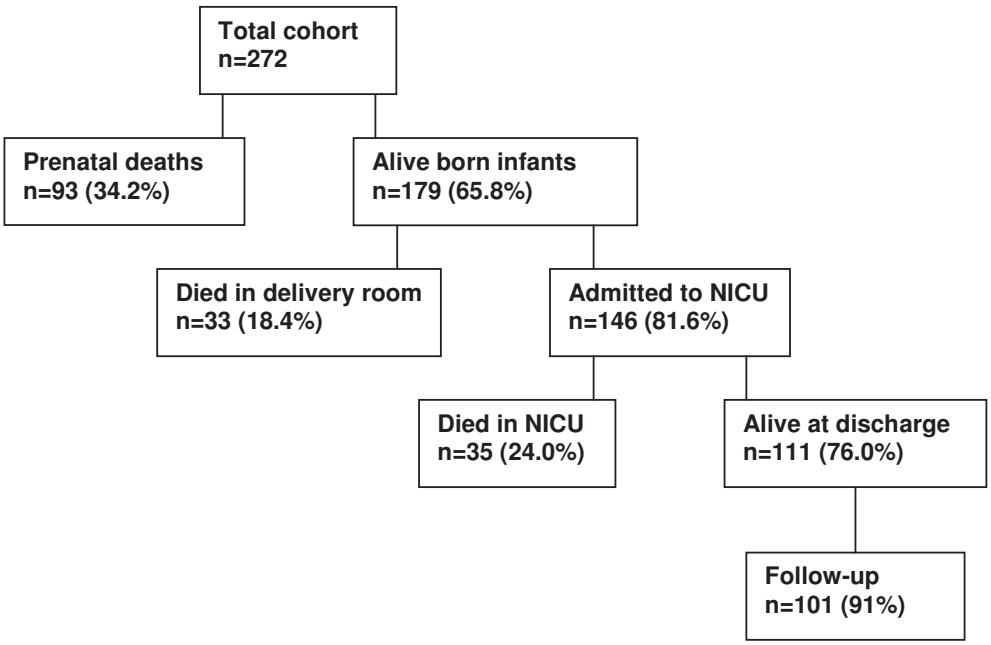
Materials and methods

Subjects

The original study population consisted of a cohort of 272 infants with a BW ≤750g and a GA of ≥24 completed weeks, born between 1996 and 2005.

Intra-uterine death occurred in 93 (34.2%) infants and 179 (65.8%) infants were born alive of whom 146 infants were admitted to the level three Neonatal Intensive Care Unit (NICU) of the Wilhelmina Children's Hospital Utrecht in the Netherlands. Thirty-five infants died in the NICU. 111 (76%) survived, these children were invited to take part in the standardized follow-up program for children born at a GA <30 weeks and/or a BW <1000g who had been admitted to our NICU (Figure 1.)

Figure 1. Study population of infants with a birth weight ≤ 750g born between 1996-2005.



Data collection and definitions

Data were collected by reviewing the medical charts. GA was based on the last menstrual period and early ultrasound examination. Parental educational levels were recorded according to the occupational classification standard of Statistics Netherlands.[39] Socio-economic status (SES) was recorded according to the zip code estimated income of The Netherlands Institute for Social Research.[40]

Perinatal events that are known to affect postnatal growth were retrospectively collected[13,17]: infant respiratory distress syndrome (IRDS) grade I to IV was

defined according to Giedion.[41] Bronchopulmonary dysplasia (BPD) was defined as the need for oxygen at 36 weeks GA according to Shennan et al.[42] Postnatal hydrocortisone use was registered. Patent ductus arteriosus (PDA) was diagnosed clinically and confirmed by cardiac ultrasound. Periventricular leukomalacia (PVL) and intraventricular haemorrhage (IVH) were graded according to de Vries et al.[43] Septicaemia was defined as clinical signs in combination with a positive blood culture. NEC was classified according to the criteria of Bell et al.[44]

The children were measured (Ht, Wt and OFC) at birth, at 15 months CA, 2 years CA, 3.5 years and 5.5 years of age. A correction for prematurity was made by subtracting the amount of prematurity (40 minus GA at birth) from the actual age at measuring and was used until two years of age.

Wt, Ht and OFC at birth were obtained for respectively 101, 96 and 97 children. At 15 months and 2 years CA Ht, Wt and OFC were obtained for respectively 92, 86 and 93 children and 95, 94 and 93 children. At 3.5 years of age Ht was measured in 59 children, Wt in 60 and OFC in 56, and at 5.5 years of age Ht and Wt were available for 70 and 69 children and OFC for 67 children.

BW was converted into SDS according to the Dutch growth curves of the Perinatal Registry of the Netherlands (PRN).[45,46] Wt for GA at the 50th percentile was used as mean and the average SD (calculated by the formula (-1SD + 1SD) / 2) was utilized. Ht and OFC at birth were converted into SDS according to the Canadian age-and sex-specific growth diagrams of Usher and McLean using Growth analyser 3.5 software (2007, Dutch Growth Foundation)[47], as GA-specific Dutch diagrams are not available. According to the cut-off levels used by endocrinologists SGA and AGA were defined as a Ht and/ or Wt at birth <-2 SDS and Ht and Wt ≥-2 SDS.[19,20]

For OFC SDS we decided to use <p10 and ≥p10 for the definition of SGA and AGA respectively, as these cut-offs have been used by others when reporting on the relation between growth and later development.[11,15,21,22]

The subsequent anthropometric measurements (Ht, weight for height (Wt/Ht), Wt and OFC) at 15 months CA, 2 years CA, 3.5 years of age and 5.5 years of age were converted into a SDS according to the Dutch age-and sex-specific growth diagrams of Fredriks et al. also using Growth analyser 3.5 software.[48] An SDS of 0 equals the age- and sex-specific mean (or 50th percentile) of the national reference population, and a SDS of -1.28 equals the 10th percentile. Wt/Ht SDS were calculated from 15 months CA onwards.

Parental heights were obtained by telephone interview, and were available for 78 children. Target height (TH) was calculated according to a Dutch population and gender specific formula: TH boys= (Ht father+Ht mother+13)/2+4.5 cm and TH girls= (Ht father+Ht mother-13)/2+4.5 cm. TH was converted into SDS (for boys (TH-184)/ 7.1 and for girls (TH-170.6)/6.5).[48] To correct for genetic growth potential, Ht SDS was also corrected for TH (SDSHtcorr) by subtracting the TH SDS from the Ht SDS (Ht SDS-TH SDS) at all test ages.

The growth patterns of SGA children were either classified as no catch-up if their growth parameters remained below the -2 SDS, or as catch-up growth indicating the achievement of Ht, Wt/Ht or Wt at or above the -2 SDS. The growth patterns of AGA children were either classified as adequate when their growth parameters remained at or above the -2 SDS, or as catch-down growth indicating a decreasing growth from ≥-2 SDS to < -2 SDS.
For OFC the growth patterns of children SGA for OFC were either classified as no catch-up if their growth parameters remained below the 10th percentile or as catch-up growth if OFC became ≥p10. The growth patterns of AGA children were either classified as adequate when their OFC remained at or above the 10th percentile, or as catch-down growth: a decrease in OFC growth from ≥p10 to <p10.
Treatment with growth hormone (GH) was registered, and children who received GH treatment (n=9) were also analysed separately. Treatment with GH was offered to children from 4 years of age onwards, with a current height <-2.5 SDS and Ht ≤-1 SD below the TH-SDS, without catch-up growth (delta height SDS ≤0) and who had a birth length and/ or Wt <-2 SDS (according to the Dutch guidelines for the treatment of children born SGA who do not show catch-up growth).[49]
The standardized follow-up program was previously described.[9,36-38] In this study we only used the results of the assessments at 5.5 years of age, which included an intelligence test and the Movement Assessment Battery for Children (M-ABC). An intelligence test was performed in 61 children, this was either the Revision Amsterdam Children's Intelligence Test (RAKIT, n=29) or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI, n=26) or the Snijders-Oomen Nonverbal Revised (SON-R, n=6) Intelligence Test. A total intelligence quotient (IQ) can be calculated from all three intelligence tests and all have a mean (±SD) score for the general population of 100 (±15).[33,50-52] The M-ABC was performed in 70 children, in this test manual dexterity, ball skills and static and dynamic balance were assessed by 8 motor tasks. In the majority of our study population the first edition of the M-ABC (n=50) was used, however in 2007 a new similar version became available and from October 2007 onwards the children in our follow-up program were assessed with the second edition: M-ABC-2 (n=20). Performance scores are calculated for these three items, as well as a total impairment score (TIS).[34, 53-55] The intelligence quotient (IQ) and TIS were converted into Z-scores. The following classification was used: normal (Z-score ≥ -1), mildly delayed (Z-score -1 to -2), or severely delayed (Z-score < -2).

Statistical analysis
To check for accuracy, data entered were double checked. All analyses were performed using SPSS (version 15.0) software (SPSS Inc., Chicago, IL, USA). Statistical comparisons for continuous variables were made with Mann-Whitney tests. Dichotomous and categorical variables were tested using Chi-square test or Fisher's exact test. SDS of anthropometric measurements at various age periods

(birth - 2 years, 2 - 3.5 years, 3.5 - 5.5 years, birth - 3.5 years and birth - 5.5 years) were compared with a Wilcoxon test. A *p* value <0.05 was considered statistically significant.
Various subjects had missing values for anthropometric measures and cognitive and motor developmental outcome. Exclusion of the subjects with missing values may yield biased results as children who are lost to follow-up are often selectively missing. We compared the characteristics of the children in whom an IQ test and motor developmental test was performed at 5.5 years of age with the children who were lost to follow-up (Tables 5. and 6.). In order to obtain all data for 101 children we imputed missing values by single imputation despite no significant differences between the non-missing and missing children.[56,57]

Results

Baseline characteristics

Table 1. shows the baseline characteristics of the 101 ELBW children who were included in the follow-up. The median BW was 675g and the median GA 28 weeks.
The 101 infants were classified as AGA or SGA based on Ht and Wt at birth (both ≥ -2 SDS or one or both < -2 SDS respectively). For evaluation of OFC a separate classification was used, based on OFC at birth (AGA ≥ p10 and SGA < p10). AGA infants had a significantly shorter GA compared to SGA infants.
Maternal hypertensive disorders were more common during the pregnancies of SGA infants. Both AGA and SGA infants were predominantly delivered by caesarean section, but the prevalence of caesareans sections was higher in SGA infants.
PDA was significantly more common in AGA children. Furthermore, in infants born AGA based on OFC, both high and low maternal educational levels were more prevalent, IRDS grade III/IV was more common and more hydrocortisone treatment was needed in AGA compared to SGA infants.[9]

Size at birth

The anthropometric measurements at birth, are presented in the Tables 2A, B, and C. For the total cohort (n=101) mean Ht, Wt and OFC SDS at birth were -4.05, -1.42, and -1.81 respectively. Ht corrected for TH is also shown in Table 2A. The mean Ht SDS and the Ht corrected for TH SDS (-4.09 at birth) do not differ much, therefore in subsequent tables we have used Ht SDS.
All anthropometric measurements at birth were significantly lower for SGA children compared to AGA children (*p*<0.001).

Postnatal growth

The postnatal anthropometric measurements at 15 months CA, 2 years CA, 3.5 years and 5.5 years of age are shown in the Tables 2A, B, C and D.

Table 1. Population characteristics and perinatal events of 101 children with a birth weight ≤750g.

		Height and/ or weight based on -2 sds at birth		Occipital-frontal circumference based on OFC p10 at birth	
	Total cohort n=101	AGA n=13	SGA n=88	AGA n=33	SGA n=68
	n (%)	n (%)	n (%)	n (%)	n (%)
Median maternal age (years) (min-max)	30.0 (17-45)	30 (27-43)	30 (17-45)	30 (19-43)	30 (17-45)
Median GA (weeks) (min-max)	28.0 (24.8-34.4)	**26.1 (25.0-27.8)**	**28.1 $ (24.8-34.4)**	**26.3 (25.0-31.0)**	**28.5 (24.8-34.4)**
Median BW (gram) (min-max)	675 (480-750)	**735 (650-750)**	**655 $ (480-750)**	**720 (580-750)**	**645 $ (480-750)**
Median birth length (cm) (min-max)	31.0 (21.0-37.0)	**31.0 (21.0-35.0)**	**33.0 $ (32.5-37.0)**	**31.0 (21-35.5)**	**33.0 $ (29.0-37.0)**
Median birth OFC (cm) (min-max)	23.2 (20.0-29.0)	23.2 (20.0-27.0)	23.3 (22.0-29.0)	**23.0 (20.0-26.0)**	**24.0 $ (22.0-29.0)**
Multiple birth	20 (19.8)	5 (38.5)	15 (17.0)	10 (30.3)	10 (14.7)
Male	45 (44.6)	6 (46.2)	39 (44.3)	16 (48.5)	29 (42.6)
Caucasian ethnicity	93 (92.1)	12 (92.3)	81 (92.0)	31 (93.9)	62 (91.2)
SES					
-high	21 (21.0)	4 (30.8)	17 (19.5)	8 (25.0)	13 (19.1)
-average	64 (64.0)	6 (46.2)	58 (66.7)	16 (50.0)	48 (70.6)
-low	15 (15.0)	3 (23.1)	12 (13.8)	8 (25.0)	7 (10.3)
Maternal educational level*					
-high	12 (17.9)	1 (12.5)	11 (18.6)	**7 (29.2)**	**5 (11.6) $**
-average	28 (41.8)	2 (25.0)	26 (44.1)	**4 (16.7)**	**24 (55.8)**
-low	27 (40.3)	5 (62.5)	22 (37.3)	**13 (54.2)**	**14 (32.6)**
Prenatal steroids	81 (86.2)	11 (84.6)	75 (85.2)	27 (81.8)	59 (86.8)
Maternal hypertensive disorder	59 (58.4)	**4 (30.8)**	**55 (62.5) $**	17 (51.5)	42 (61.8)
Caesarean delivery	83 (82.2)	**6 (46.2)**	**77 (87.5) $**	**20 (60.6)**	**63 (92.6) $**
5-min Apgar score <7	12 (11.9)	**4 (30.8)**	**8 (9.1) $**	6 (18.2)	6 (8.8)

		Height and/ or weight		Occipital-frontal circumference	
		based on -2 sds at birth		based on OFC p10 at birth	
	Total cohort n=101	**AGA n=13**	**SGA n=88**	**AGA n=33**	**SGA n=68**
	n (%)	n (%)	n (%)	n (%)	n (%)
BPD	57 (56.4)	9 (69.2)	48 (54.5)	23 (69.7)	34 (50.0)
Hydrocortisone treatment	50 (49.5)	7 (53.8)	43 (48.9)	**22 (66.7)**	**28 (41.2) $**
Septicaemia	62 (61.4)	8 (61.5)	54 (61.4)	17 (51.5)	45 (66.2)
NEC	9 (8.9)	1 (7.7)	8 (9.1)	2 (6.1)	7 (10.3)
PDA	34 (33.7)	**9 (69.2)**	**25 (28.4) $**	**16 (48.5)**	**18 (26.5) $**
IVH grade III/IV	4 (4.0)	0	4 (4.5)	1 (3.0)	3 (4.4)
Cystic PVL	0	0	0	0	0

Total cohort: children born in 1996-2005. AGA: appropriate for gestational age: height (Ht) and weight (Wt) at birth ≥ -2 sds, SGA: small for gestational age: Ht and/ or Wt at birth <-2 sds. Occipital-Frontal Circumference at birth: AGA ≥p10 and SGA <p10. SES: socio-economic status, *maternal educational level was available for n=67, 21/101 indicated to be a house-wife. Maternal hypertensive disorder: gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome. IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, IVH: intraventricular haemorrhage, PVL: periventricular leukomalacia. $ and bold indicates $p < 0.05$ for comparison of AGA and SGA within Ht and/or Wt at birth or OFC at birth.

Height

Mean Ht SDS remained significantly lower for SGA children at 15 months and 2 years CA.

Five age periods were compared (birth to 2 years CA, 2 years CA to 3.5 years, 3.5 to 5.5 years, birth to 3.5 years and birth to 5.5 years of age) for the total cohort, AGA and SGA children. Ht SDS significantly increased for the total cohort and for SGA children between all age periods (p<0.001), except for the period between 2 years CA and 3.5 years of age. Moreover, the mean Ht SDS of AGA children decreased in this period (p=0.027).

Of the 101 children 9 (8.9%) received GH treatment from 4 years of age onwards. The mean Ht SDS of these 9 children was still significantly lower at 5.5 years of age compared to the 92 children who did not receive GH treatment (-2.49 vs -1.19, p<0.001, data not shown).

Weight for Height

Comparison of AGA and SGA children showed that the mean Wt/Ht SDS of SGA children was only significantly lower at 2 years CA (Table 2B). Wt/Ht SDS significantly increased for SGA children between 2 years CA and 3.5 years of age (p=0.018).

Weight

Mean Wt SDS was significantly lower for SGA children at 15 months CA and 2 years of age (Table 2C).

Between birth and 2 years CA Wt SDS significantly decreased for the total cohort, as well as for SGA children (p <0.001). Furthermore, between birth and 3.5 years of age Wt SDS significantly decreased for the total cohort, AGA and SGA children separately (p<0.001, p=0.048 and p=0.007 respectively).

Occipital-Frontal Circumference

Mean OFC SDS remained significantly lower for SGA children at all ages (Table 2D). OFC SDS significantly increased for SGA children between birth and 2, 3.5 and 5.5 years of age (p<0.001) and for the total cohort between birth and 3.5 and 5.5 years of age (p<0.001).

Table 2a. Postnatal growth in height of children with a birth weight ≤ 750g.

	Total cohort n=101 mean Z-score SD (min~max)	AGA n=13 mean Z-score SD (min~max)	SGA n=88 mean Z-score SD (min~max)	AGA vs SGA p-value	birth – 2yr[A] 2yr – 3.5yr[B] 3.5yr – 5.5yr[C] birth – 3.5yr[D] birth – 5.5yr[E] p-value
Ht sds birth	-4.05	-1.12	-4.48	**<0.001**	
	(1.9, -11.08~ -0.02)	(0.7, -1.92~ -0.02)	(1.6, -11.08~ -2.02)		TC,SGA <0.001[A] AGA ≥ 0.05[A]
Ht sds 15m CA	-1.84	-1.13	-1.95	**0.019**	
	(1.3, -6.11~0.98)	(1.0, -3.09~0.59)	(1.3, -6.11~0.98)		TC,SGA ≥ 0.05[B] AGA 0.027[B]
Ht sds 2yr CA	-1.53	-0.82	-1.64	**0.021**	
	(1.2, -4.48~1.81)	(1.1, -3.02~1.25)	(1.2, -4.48~1.81)		TC,SGA <0.001[C] AGA ≥0.05[C]
Ht sds 3.5 yr	-1.62	-1.22	-1.68	0.225	
	(1.2, -5.55~1.10)	(1.0, -3.04~1.10)	(1.2, -5.55~0.70)		TC,SGA <0.001[D] AGA ≥ 0.05[D]
Ht sds 5.5 yr	-1.31	-1.22	-1.32	0.677	
	(1.0, -4.34~0.69)	(0.9, -2.96~0.09)	(1.1, -4.34~0.69)		TC,SGA <0.001[E] AGA ≥ 0.05[E]
TH sds	0.04	-0.08	0.06	0.614	
	(0.9, -2.25~2.04)	(0.9, -1.55~1.22)	(0.8, -2.25~2.04)		
sdsHtcorr birth	-4.09	-1.05	-4.54	**<0.001**	
	(2.0, -10.68~ -0.18)	(0.8, -3.14~ -0.18)	(1.7, -10.68~ -0.61)		
sdsHtcorr 15m CA	-1.88	-1.05	-2.00	**0.028**	
	(1.4, -6.18~1.57)	(1.4, -3.51~1.57)	(1.3, -6.18~0.70)		
sdsHtcorr 2 yr CA	-1.57	-0.75	-1.70	**0.008**	
	(1.3, -5.33~1.28)	(1.2, -2.99~1.12)	(1.3, -5.33~1.28)		
sdsHtcorr 3.5 yr	-1.67	-1.15	-1.74	0.123	
	(1.3, -6.96~1.50)	(1.3, -3.02~ 1.50)	(1.3, -6.96~0.91)		
sdsHtcorr 5.5 yr	-1.35	-1.15	-1.38	0.685	
	(1.1, -4.47~1.33)	(1.2, -2.84~ 1.33)	(1.1, -4.47~0.75)		

Total cohort: children born in 1996-2005, AGA: appropriate for gestational age: height (Ht) and weight (Wt) at birth ≥ -2sds, SGA: small for gestational age: Ht and/ or Wt at birth <-2sds. Ht SDS at birth based on growth curves of Usher and McLean.[47] Subsequent SDS based on Dutch growth curves of Fredriks et al.[48] Ht: height, TH: target height, sdsHtcorr: Ht corrected for TH= Htsds-THsds. CA: corrected age, UCA: uncorrected age. AGA vs SGA analyzed with Chi-square and A, B, C, D, E analyzed with Wilcoxon test. TC: total cohort. For missing values single imputation was used.

Table 2b. Postnatal growth in weight for height of children with a birth weight ≤ 750g.

	Total cohort n=101	AGA n=13	SGA n=88	AGA vs SGA	15m – 2yr[A] 2yr – 3.5yr[B] 3.5yr – 5.5yr[C] 15m – 3.5yr[D] 15m – 5.5yr[E]
	mean Z-score SD (min~max)	mean Z-score SD (min~max)	mean Z-score SD (min~max)	p-value	p-value
15 months CA	-1.26 (1.2, -4.35~1.25)	-0.77 (1.2, -2.61~1.25)	-1.33 (1.2, -4.35~ 1.21)	0.153	TC,SGA, AGA ≥0.05[A]
2 years CA	-1.31 (1.4, -5.78~2.16)	-0.65 (1.0, -2.36~0.76)	-1.41 (1.4, -5.78~ 2.16)	**0.047**	TC,AGA ≥0.05[B] SGA 0.018[B]
3.5 years UCA	-1.10 (1.2, -4.09~2.63)	-0.80 (0.9, -2.17~0.43)	-1.14 (1.2, -4.09~ 2.63)	0.378	TC,AGA,SGA ≥0.05[C]
5.5 years UCA	-0.99 (1.2, -3.81~2.82)	-0.51 (0.9, -1.94~0.97)	-1.06 (1.2, -3.81~2.82)	0.076	TC,SGA, AGA ≥0.05[D] TC,SGA, AGA ≥0.05[E]

Total cohort: children born in 1996-2005, AGA: appropriate for gestational age: height (Ht) and weight (Wt) at birth ≥ -2sds, SGA: small for gestational age: Ht and/ or Wt at birth <-2sds. Weight for height (Wt/Ht) SDS based on Dutch growth curves of Fredriks et al.[48] CA: corrected age, UCA: uncorrected age. AGA vs SGA analyzed with Chi-square and A, B, C, D, E analyzed with Wilcoxon test. TC: total cohort. For missing values single imputation was used.

Table 2c. Postnatal growth in weight of children with a birth weight ≤ 750g.

	Total cohort n=101	AGA n=13	SGA n=88	AGA vs SGA	birth – 2yr[A] 2yr – 3.5yr[B] 3.5yr – 5.5yr[C] birth – 3.5yr[D] birth – 5.5yr[E]
	mean Z-score SD (min~max)	mean Z-score SD (min~max)	mean Z-score SD (min~max)	p-value	p-value
Birth	-1.42	-0.53	-1.55	**<0.001**	
	(0.8, -3.67~ 0.35)	(0.6, -1.44~ 0.35)	(0.7, -3.67~ -0.31)		TC, SGA <0.001[A] AGA ≥0.05[A]
15 months CA	-2.01	-1.17	-2.14	**0.014**	
	(1.4, -5.81~2.21)	(1.1, -2.95~0.57)	(1.4, -5.81~ 2.21)		TC,AGA,SGA ≥0.05[B]
2 year CA	-1.79	-0.95	-1.91	**0.010**	
	(1.3, -6.22~1.34)	(1.1, -3.11~0.31)	(1.3, -6.22~ 1.34)		TC,AGA,SGA ≥0.05[C]
3.5 year UCA	-1.75	-1.28	-1.83	0.068	
	(1.2, -5.10~1.87)	(1.0, -3.03~0.30)	(1.2, -5.10~ 1.87)		TC,<0.001, SGA 0.007[D] AGA 0.048[D]
5.5 year UCA	-1.58	-1.05	-1.66	0.065	
	(1.2, -4.96~2.09)	(1.1, -3.26~0.83)	(1.2, -4.96~ 2.09)		TC, AGA,SGA ≥0.05[E]

Total cohort: children born in 1996-2005, AGA: appropriate for gestational age: height (Ht) and weight (Wt) at birth ≥ -2sds, SGA: small for gestational age: Ht and/ or Wt at birth <-2sds. Wt SDS at birth based on growth curves of the PRN.[45,46] Subsequent SDS based on Dutch growth curves of Fredriks et al.[48] CA: corrected age, UCA: uncorrected age. AGA vs SGA analyzed with Chi-square and A, B, C, D, E analyzed with Wilcoxon test. TC: total cohort. For missing values single imputation was used.

Table 2d. Postnatal growth in Occipital-Frontal Circumference of children with a birth weight ≤ 750g.

	Total cohort n=101	AGA n=33	SGA n=68	AGA vs SGA	birth – 2yr[A] 2yr – 3.5yr[B] 3.5yr – 5.5yr[C] birth-3.5yr[D] birth- 5.5yr[E]
	mean Z-score SD (min~max)	mean Z-score SD (min~max)	mean Z-score SD (min~max)	p-value	p-value
Birth	-1.81 (1.5, -5.36~2.86)	-0.26 (1.0, -1.21~ 2.86)	-2.57 (0.9, -5.36~ -1.32)	**<0.001**	TC,SGA <0.001[A] AGA ≥0.05[A]
15 months CA	-1.20 (1.1, -4.94~1.59)	-0.70 (1.4, -4.94~1.59)	-1.45 (0.9, -3.11~0.44)	**<0.001**	TC,AGA,SGA ≥0.05[B]
2 year CA	-1.10 (1.0, -3.84~1.06)	-0.57 (1.1, -2.64~1.06)	-1.35 (0.9, -3.84~0.75)	**<0.001**	TC,AGA ≥0.05[C]
3.5 year UCA	-1.12 (1.0, -3.94~1.20)	-0.59 (0.9, -2.03~1.20)	-1.38 (0.9, -3.94~0.49)	**<0.001**	SGA 0.048[C]
5.5 year UCA	-1.04 (0.9, -2.78~1.16)	-0.53 (0.8, -2.23~1.16)	-1.28 (0.8, -2.78~0.33)	**<0.001**	TC,SGA <0.001[D] AGA≥0.05[D]
					TC,SGA <0.001[E] AGA ≥0.05[E]

Total cohort: children born in 1996-2005, AGA: appropriate for gestational age: Occipital- Frontal Circumference (OFC) at birth ≥p10. SGA: small for gestational age: OFC at birth <p10. SDS at birth based on growth curves of Usher and McLean.[47]. Subsequent SDS based on Dutch growth curves of Fredriks et al.[48] CA: corrected age, UCA: uncorrected age. AGA vs SGA analyzed with Chi-square and A, B, C, D, E analyzed with Wilcoxon test. TC: total cohort. For missing values single imputation was used.

Growth between birth and 2 years corrected age
The change in growth classification between birth and 2 years CA is presented in Table 3A. Catch-up growth in Ht, Wt/Ht and Wt (to ≥-2 SDS) occurred in respectively 60.2%, 72.7% and 59.1% of the 88 SGA children. Catch-up growth in OFC (to ≥p10) occurred in 36.8% of the 68 SGA for OFC children.
Catch-down growth for Wt occurred in 23.1% of the AGA children, whereas the majority of the AGA children showed adequate growth in Ht (84.6%), Wt/Ht (92.3%). For OFC, catch-down growth occurred in 21.2% of the OFC-AGA children.

Growth between 2 years CA and 3.5 years of age
The change in growth classification between 2 years CA and 3.5 years of age is presented in Table 3B. Catch-up growth in Ht between 2 and 3.5 years occurred in 9 children (all SGA), for Wt/Ht in 16 (15 SGA) and for Wt in 10 children (all SGA). Catch up in OFC occurred in 8 children (6 OFC-SGA). Catch-down growth was found for Ht in 10 children (9 SGA), for Wt/Ht in 9 (8 SGA) and for Wt in 8 children (all SGA). Catch-down for OFC was detected in 10 children, (6 OFC-SGA). When all changes between 2 and 3.5 yrs are analyzed, most of the catch-up as well as “catch-down” was noticed in the group of SGA children for Ht, Wt/Ht and Wt (data not shown).

Growth between 3.5 and 5.5 years of age
The change in growth classification between 3.5 and 5.5 years of age is presented in Table 3C. Catch-up growth in Ht between 3.5 and 3.5 years occurred in 15 children (14 SGA), for Wt/Ht in 7 (6 SGA) and for Wt in 3 children (all SGA). Catch-up growth in OFC occurred in 13 children (9 OFC-SGA). Catch-down growth in Ht was found in 3 children (all SGA), in Wt/Ht in 7 (all SGA) and in Wt in 8 children (7 SGA). OFC showed catch-down growth in 5 children (4 OFC-SGA). When all changes between 3.5 and 5.5 yrs are analyzed, for both catch-up as well as “catch-down” most changes were noticed in the group of SGA children. (data not shown).

Growth between birth and 5.5 years of age
The change in growth classification between birth and 5.5 years of age is presented in Table 3A. The majority of the SGA children have caught up in Ht and Wt/Ht at this time point (72.7% and 79.5% respectively), whereas 43.2% of the SGA children did not show lasting catch-up growth in Wt. 55.9% of the OFC- SGA children did not show lasting catch-up growth in OFC. A substantial part (30.8%) of the AGA children displayed catch-down growth in Wt, whereas most of the AGA children retained adequate growth in Ht and Wt/Ht. (84.6% and 100% respectively). For OFC adequate growth was also remained in OFC-AGA children (81.8%).

Table 3a. Change in growth classification from birth to 2 years CA, birth to 3.5 years and birth to 5.5 years of age.

Classification of growth at birth		2 yr CA, n (%)		3.5 yr, n (%)		5.5 yr, n (%)	
		insufficient	adequate	insufficient	adequate	insufficient	adequate
Ht	SGA (n=88)	35 (39.8) [a]	53 (60.2) [b]	35 (39.8) [a]	53 (60.2) [b]	24 (27.3) [a]	64 (72.7) [b]
	AGA (n=13)	2 (15.4) [c]	11 (84.6) [d]	3 (23.1) [c]	10 (76.9) [d]	2 (15.4) [c]	11 (84.6) [d]
	Total	37	64	38	63	26	75
Wt/Ht	SGA (n=88)	24 (27.3) [a]	64 (72.7) [b]	17 (19.3) [a]	71 (80.7) [b]	18 (20.5) [a]	70 (79.5) [b]
	AGA (n=13)	1 (7.7) [c]	12 (92.3) [d]	1 (7.7) [c]	12 (92.3) [d]	0 [c]	13 (100) [d]
	Total	25	76	18	83	18	83
Wt	SGA (n=88)	36 (40.9) [a]	52 (59.1) [b]	34 (38.6) [a]	54 (61.4) [b]	38 (43.2) [a]	50 (56.8) [b]
	AGA (n=13)	3 (23.1) [c]	10 (76.9) [d]	3 (23.1) [c]	10 (76.9) [d]	4 (30.8) [c]	9 (69.2) [d]
	Total	39	62	37	64	42	59
OFC	< p10 (n=68)	43 (63.2) [a]	25 (36.8) [b]	43 (63.2) [a]	25 (36.8) [b]	38 (55.9) [a]	30 (44.1) [b]
	≥ p10 (n=33)	7 (21.2) [c]	26 (78.8) [d]	9 (27.3) [c]	24 (72.7) [d]	6 (18.2) [c]	27 (81.8) [d]
	Total	50	51	52	49	44	57

Ht: height, Wt/Ht: weight for height, Wt: weight, OFC: Occipital-Frontal Circumference, percentages are row percentages. AGA: appropriate for gestational age: Ht and Wt at birth ≥ -2sds, SGA: small for gestational age: Ht and/ or Wt at birth <-2sds. For Ht, Wt and Wt/Ht insufficient: <-2sds, adequate: ≥-2sds, [a] no catch-up growth: remained <-2sds, [b] catch-up growth: <-2sds to ≥-2sds, [c] catch-down growth: ≥-2sds to <-2sds, [d] adequate growth: remained ≥-2sds. For OFC insufficient: <p10, adequate: ≥p10, [a] no catch-up growth: remained <p10, [b] catch-up: <p10 to ≥p10, [c] catch-down: ≥p10 to <p10, [d] adequate: remained ≥p10.

Table 3b. Change in growth classification from 2 to 3.5 year.

Classification of growth at 2 yr		Classification of growth at 3.5 yr, n (%)		
		insufficient	adequate	Total
Ht	< -2 sds	28 (75.7) [a]	9 (24.3) [b]	37
	≥ -2 sds	10 (15.6) [c]	54 (84.4) [d]	64
	Total	38	63	101
Wt/Ht	< -2 sds	9 (36.0) [a]	16 (64.0) [b]	25
	≥ -2 sds	9 (11.8) [c]	67 (88.2) [d]	76
	Total	18	83	101
Wt	< -2 sds	29 (74.4) [a]	10 (25.6) [b]	39
	≥ -2 sds	8 (12.9) [c]	54 (87.1) [d]	62
	Total	37	64	101
OFC	< p10	42 (84.0) [a]	8 (16.0) [b]	51
	≥ p10	10 (19.6) [c]	41 (80.4) [d]	50
	Total	52	49	101

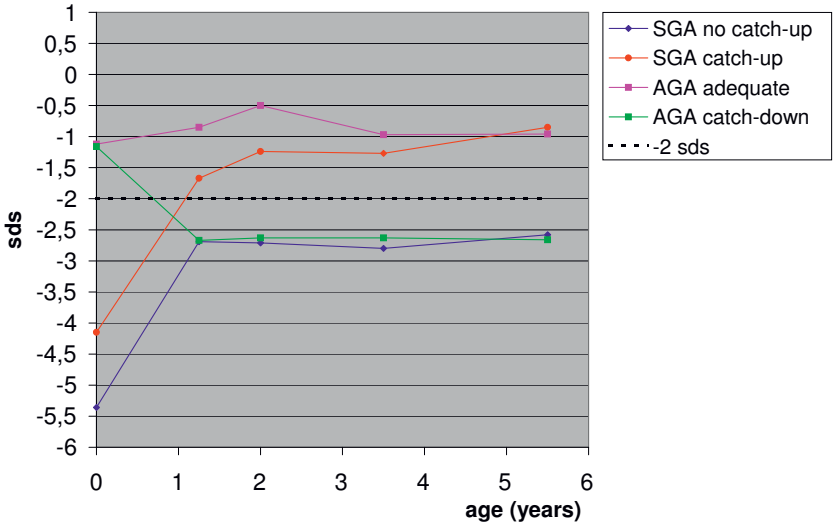
Ht: height, Wt/Ht: weight for height, Wt: weight, OFC: Occipital-Frontal Circumference. Percentages are row percentages. For Ht, Wt and Wt/Ht insufficient: <-2sds, adequate: ≥-2sds, [a] no catch-up growth: remained <-2sds, [b] catch-up growth: <-2sds to ≥-2sds, [c] catch-down growth: ≥-2sds to <-2sds, [d] adequate growth: remained ≥-2sds. For OFC insufficient: <p10, adequate: ≥p10, [a] no catch-up growth: remained <p10, [b] catch-up: <p10 to ≥p10, [c] catch-down: ≥p10 to <p10, [d] adequate: remained ≥p10.

Table 3c. Change in growth classification from 3.5 to 5.5 year.

Classification of growth at 3.5 yr		Classification of growth at 5.5 yr, n (%)		
		insufficient	adequate	Total
Ht	< -2 sds	23 (60.5) [a]	15 (39.5) [b]	38
	≥ -2 sds	3 (4.8) [c]	60 (95.2) [d]	63
	Total	26	75	101
Wt/Ht	< -2 sds	11 (61.1) [a]	7 (38.9) [b]	18
	≥ -2 sds	7 (8.4) [c]	76 (91.6) [d]	83
	Total	18	83	101
Wt	< -2 sds	34 (91.9) [a]	3 (8.1) [b]	37
	≥ -2 sds	8 (12.5) [c]	56 (87.5) [d]	64
	Total	42	59	101
OFC	< p10	39 (75.0) [a]	13 (25.0) [b]	52
	≥ p10	5 (10.2) [c]	44 (89.8) [d]	49
	Total	44	57	101

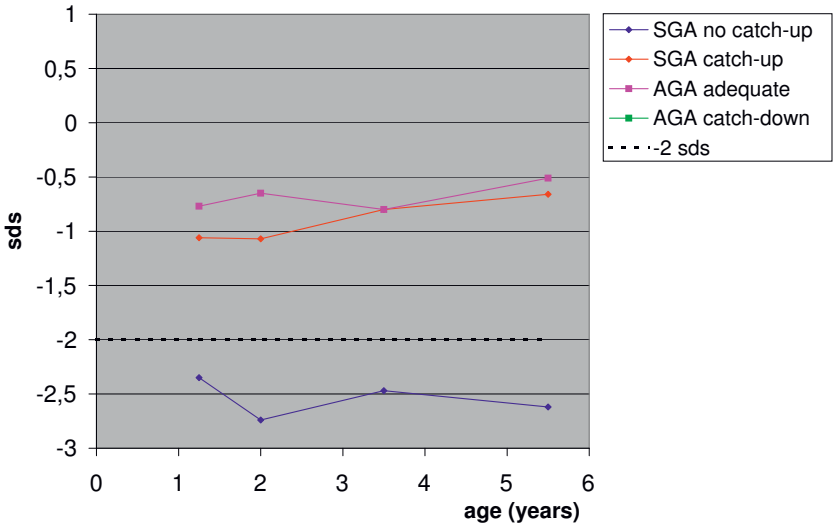
Ht: height, Wt/Ht: weight for height ,Wt: weight, OFC: Occipital-Frontal Circumference. Percentages are row percentages. For Ht, Wt and Wt/Ht insufficient: <-2sds, adequate: ≥-2sds, [a] no catch-up growth: remained <-2sds, [b] catch-up growth: <-2sds to ≥-2sds, [c] catch-down growth: ≥-2sds to < -2sds, [d] adequate growth: remained ≥-2sds. For OFC insufficient: <p10, adequate: ≥p10, [a] no catch-up: remained <p10, [b] catch-up: <p10 to ≥p10, [c] catch-down: ≥p10 to <p10, [d] adequate: remained ≥p10.

Figure 2a. Height growth patterns of 101 children BW ≤ 750g between birth and 5.5 years of age.



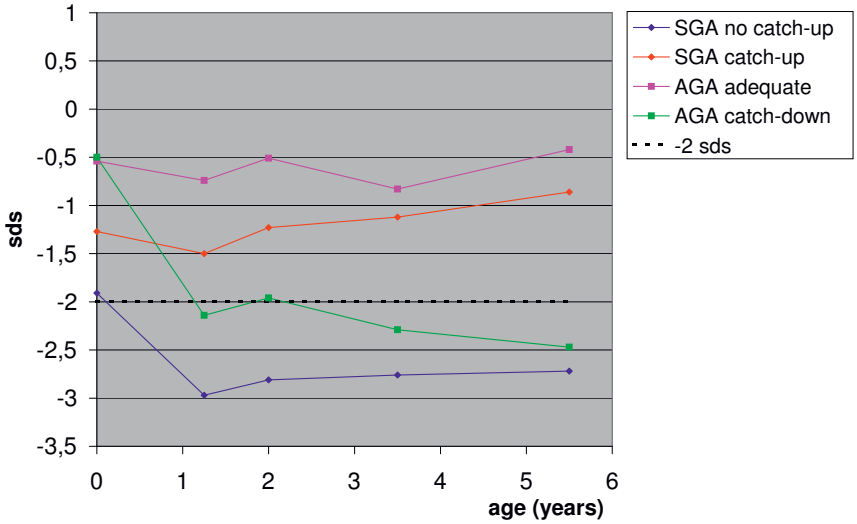
Mean height (Ht) sds for different patterns of postnatal growth between birth and 5.5 yr. SGA: small for gestational age: Ht and/ or weight (Wt) at birth <-2sds, AGA: appropriate for gestational age: Ht and Wt at birth ≥ -2sds. No catch-up growth (n=24): remained <-2 sds, catch-up (n=64): <-2sds to ≥-2sds, adequate (n=11): remained ≥-2sds, catch-down (n=2): ≥-2sds to <-2sds.

Figure 2b. Weight for height growth patterns of 101 children BW ≤ 750g between 15 months CA and 5.5 years of age.



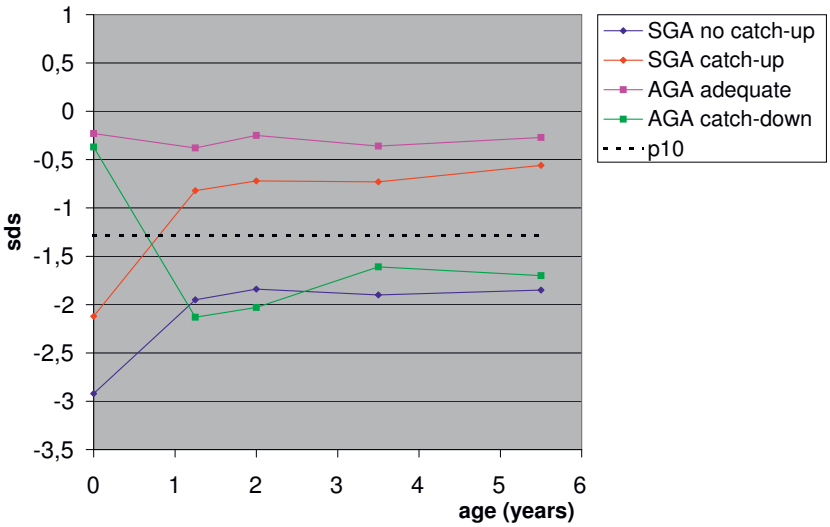
Mean weight for height (Wt/Ht) sds for different patterns of postnatal growth between 15 months corrected age (CA) and 5.5 yr. SGA: small for gestational age: height (Ht) and/ or weight (Wt) at birth <-2sds, AGA: appropriate for gestational age: Ht and Wt at birth ≥ -2sds. No catch-up growth (n=18): remained <-2sds, catch-up (n=70): <-2sds to ≥-2sds, adequate (n=13): remained ≥-2sds, catch-down (n=0): ≥-2sds to <-2sds.

Figure 2c. Weight growth patterns of 101 children BW ≤ 750g between birth and 5.5 years of age.



Mean weight (Wt) sds for different patterns of postnatal growth between birth and 5.5 years of age. SGA: small for gestational age: height (Ht) and/ or Wt at birth <-2 sds, AGA: appropriate for gestational age: Ht and Wt at birth ≥-2sds. No catch-up growth (n=38): remained <-2sds, catch-up (n=50): <-2sds to ≥-2sds, adequate (n=9): remained ≥-2sds, catch-down (n=4): ≥-2sds to <-2sds.

Figure 2d. Occipital-Frontal Circumference growth patterns of 101 children BW ≤ 750g between birth and 5.5 years of age.



Mean Occipital-Frontal Circumference (OFC) sds for different patterns of postnatal growth between birth and 5.5 years of age. SGA: small for gestational age: OFC <p10 at birth, AGA: appropriate for gestational age: OFC ≥p10 at birth. No catch-up growth (n=38): remained <p10, catch-up (n=30): <p10 to ≥p10, adequate (n=27): remained ≥p10, catch-down (n=6): ≥p10 to <p10.

Postnatal growth patterns

The different growth patterns of SGA and AGA children between birth and 5.5 years of age are depicted in Figures 2A, 2B, 2C and 2D. For Ht, Wt/Ht and Wt SGA children either caught-up to ≥ -2 SDS, or showed no catch-up growth and remained < -2 SDS. AGA children either displayed adequate growth and remained ≥ -2 SDS , or showed catch-down growth to <-2 SDS at 5.5 years of age.

Figure 2A. illustrates that catch-up growth in Ht of SGA children and catch-down growth in Ht of AGA children both took place in the first year of life. Furthermore, SGA children who caught up in Ht reached the line of AGA children with adequate growth between 3.5 and 5.5 years of age.

Figure 2C. depicts the Wt growth pattern. The graph of the SGA children who showed catch-up growth starts at a mean BW SDS of -1.27, and thus above the -2 SDS line. This is due to the definition of SGA (Ht and/ or Wt at birth < -2 SDS), which was most strongly determined by Ht at birth.

Figure 2D. presents the OFC growth patterns in which children SGA for OFC caught-up to an OFC ≥ p10 in 44.1%. The growth of AGA children mostly remained adequate ≥ p10 (81.8%). This figure illustrates that catch-up growth and catch-down growth in OFC both took place in the first year of life. The graphs of SGA children who caught-up and AGA children with adequate growth run closely from 15 months CA onwards, the same holds true for the graphs of SGA children without catch-up and AGA who displayed catch-down growth.

SGA insufficient compared to SGA catch-up growth

We analyzed possible differences in perinatal characteristics and neonatal morbidity between the two different growth patterns of SGA children. SGA children who displayed catch-up growth (Ht, Wt/Ht, Wt) had a significantly higher median BW compared to the SGA children who did not catch-up. SGA children who caught-up Ht had significantly greater length and OFC at birth compared to the SGA children who did not catch-up. SGA children who caught-up in Wt had a significantly shorter GA, more IRDS and more PVL grade I compared to SGA children without catch-up growth. Apart from this, the SGA children did not differ in GA, maternal characteristics or neonatal morbidity (Appendix Tables 8a,b,c,d).

AGA adequate compared to AGA catch-down growth

We also analyzed possible differences in perinatal characteristics and neonatal morbidity between the two different growth patterns of AGA children. AGA children who displayed catch-down growth in Ht had a significantly shorter median GA compared to the AGA children who remained adequate. Furthermore, a trend of a lower median BW was found in the OFC-AGA children with catch-down growth in OFC 650g vs 725g, p=0.065). However, the AGA children did not differ in maternal characteristics or neonatal morbidity (Appendix Tables 9a,b,c,d).

Cognitive and motor developmental outcome and postnatal growth patterns
At 5.5 years of age cognitive development was assessed by means of an IQ test and motor development by means of the M-ABC. These results together with the growth patterns between birth and 5.5 years of age are presented in Table 4. The majority (76.2%) of the 101 children had a normal cognitive developmental outcome, 16.8% a mildly delayed and 6.9% a severely delayed cognitive outcome, whereas a normal motor developmental outcome was found in only 41.6% of the children, 28.7% had a mildly delayed and 29.7% a severely delayed motor outcome.[37,38]

Height growth pattern
No significant differences in cognitive and motor developmental outcome were found between the Ht growth patterns of SGA and AGA children. Normal cognitive outcome ranged from 63.6% for AGA children with adequate growth to 78.1% for SGA children with catch-up growth. Normal motor developmental outcome ranged from 37.5% for SGA children with insufficient growth to 45.5% for AGA with adequate growth.

Weight for height growth pattern
No significant differences in cognitive developmental outcome were found between the Wt/Ht growth patterns of SGA and AGA children. Significantly more SGA children without catch-up growth had a severely delayed motor developmental outcome compared to SGA children with catch-up growth (55.6% vs 22.9%, p=0.008).

Weight growth pattern
Cognitive developmental outcome did not differ between the four Wt growth patterns. Although a trend was shown for a higher percentage of normal cognitive developmental outcome in SGA children with catch-up growth compared to SGA children without catch-up growth (84% versus 68.4% respectively).
Motor development was not different between the two types of SGA children.
There was a trend for more AGA children with catch-down growth who had a severely delayed motor outcome (75% vs 11.1%, p= 0.110 respectively), however numbers were small.

OFC growth pattern
No significant differences were found in cognitive outcome between the four different OFC growth patterns. There was a trend for a higher percentage of normal cognitive outcome in OFC-SGA children with catch-up growth compared to SGA children with insufficient growth (86.7% vs 68.4% respectively, p=0.092). Also no significant difference in motor outcome was found between the two types of OFC-SGA children, whereas significantly more AGA children with catch-down growth of OFC had a severely delayed motor outcome (66.7% vs 11.1% respectively, p=0.015).

Table 4. Postnatal growth pattern between birth and 5.5 years of age and cognitive and motor developmental outcome at age 5.5.

	SGA			AGA		
Height	**No catch-up growth**	**Catch-up growth**	**No catch-up vs catch-up**	**Adequate growth**	**Catch-down growth**	**Adequate vs catch-down**
	n=24	**n=64**	p-value	**n=11**	**n=2**	p-value
Cognitive development						
Normal	18 (75.0)	50 (78.1)	0.680	7 (63.6)	2 (100)	1.000
Mildly delayed	5 (20.8)	9 (14.1)		3 (27.3)	0	
Severely delayed	1 (4.2)	5 (7.8)		1 (9.1)	0	
Motor development						
Normal	9 (37.5)	28 (43.8)	0.870	5 (45.5)	0	0.154
Mildly delayed	7 (29.2)	18 (28.1)		4 (36.4)	0	
Severely delayed	8 (33.3)	18 (28.1)		2 (18.2)	2 (100)	
Weight for Height	**No catch-up**	**Catch-up**	**No catch-up vs catch-up**	**Adequate**	**Catch-down**	**Adequate vs catch-down**
	n=18	**n=70**	p-value	**n=13**	**n=0**	p-value
Cognitive development						
Normal	15 (83.3)	53 (75.7)	0.301	9 (69.2)	0	-
Mildly delayed	1 (5.6)	13 (18.6)		3 (23.1)	0	
Severely delayed	2 (11.1)	4 (5.7)		1 (7.7)	0	
Motor development						
Normal	7 (38.9)	30 (42.9)	**0.008**	5 (38.5)	0	-
Mildly delayed	1 (5.6)	24 (34.3)		4 (30.8)	0	
Severely delayed	10 (55.6)	16 (22.9)		4 (30.8)	0	

	SGA			AGA		
Weight	**No catch-up growth**	**Catch-up growth**	**No catch-up vs catch-up**	**Adequate growth**	**Catch-down growth**	**Adequate vs catch-down**
	n=24	**n=64**	p-value	**n=11**	**n=2**	p-value
Cognitive development						
Normal	26 (68.4)	42 (84.0)	0.189	6 (66.7)	3 (75.0)	0.169
Mildly delayed	9 (27.3)	5 (10.0)		3 (33.0)	0	
Severely delayed	3 (7.9)	3 (6.0)		0	1 (25.0)	
Motor development						
Normal	15 (39.5)	22 (44.0)	0.415	4 (44.4)	1 (25.0)	0.110
Mildly delayed	9 (23.7)	16 (32.0)		4 (44.4)	0	
Severely delayed	14 (36.8)	12 (24.0)		1 (11.1)	3 (75.0)	
OFC	**No catch-up**	**Catch-up**	**No catch-up vs catch-up**	**Adequate**	**Catch-down**	**Adequate vs catch-down**
	n=38	**n=30**	p-value	**n=27**	**n=6**	p-value
Cognitive development						
Normal	26 (68.4)	26 (86.7)	0.120	20 (74.1)	5 (83.3)	0.429
Mildly delayed	8 (21.1)	4 (13.3)		5 (18.5)	0	
Severely delayed	4 (10.5)	0		2 (7.4)	1 (16.7)	
Motor development						
Normal	16 (42.1)	10 (33.3)	0.148	14 (51.9)	2 (33.3)	**0.015**
Mildly delayed	7 (18.4)	12 (40.0)		10 (37.0)	0	
Severely delayed	15 (39.5)	8 (26.7)		3 (11.1)	4 (66.7)	

For height (Ht), weight for height (Wt/Ht) and weight (Wt): SGA: small for gestational age: Ht and/ or Wt at birth <-2sds, AGA: appropriate for gestational age: mHt and Wt at birth ≥ -2sds, no catch-up growth: remained <-2sds, catch-up growth: <-2sds to ≥-2sds, catch-down growth: ≥-2sds to <-2sds, adequate growth: mremained ≥-2sds. For Occipital-Frontal Circumference (OFC): SGA: small for gestational age: OFC <p10 at birth, AGA: appropriate for gestational age: OFC ≥p10 at birth. No catch-up: remained <p10, catch-up: <p10 to ≥p10, catch-down: ≥p10 to <p10, adequate: remained ≥p10. Cognitive development: IQ, motor development: Movement-ABC Total Impairment Score. Normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2.

Discussion

It is clear from the results of this study that ELBW children with a BW ≤ 750g show significant deficits in Ht, Wt/Ht, Wt and OFC in early childhood. Even at school age the mean SDS of all anthropometric measurements was below zero.

Ht SDS of SGA children as well as OFC SDS in OFC-SGA children significantly increased over the studied age periods (0-2yr, 3.5-5.5yr, 0-3.5yr and 0-5.5yr), whereas Wt SDS significantly decreased between birth and 2 years CA for both the total cohort and SGA children. In comparison with AGA children, OFC-SGA children persisted to have a significantly smaller OFC up to 5.5 years of age.

In our cohort catch-up growth between birth and 5.5 years of age was found in 72.2% (Ht), 79.5% (Wt/Ht) and 56.8% (Wt) of the SGA children. 44.1% showed catch-up growth in OFC in the OFC-SGA children. Catch-up growth occurred mostly between birth and 2 years CA, but after this time point the number of children with catch-up still increased, whereas some children showed temporarily catch-down growth with subsequent catch-up. The growth parameters in which the least catch-up growth was shown, also had the highest percentage of catch-down growth (30.8% in Wt and 18.2% in OFC).

Hokken-Koelega et al. have shown that the majority (82.5%) of the preterm born SGA children (SGA defined as birth length <p3 for GA) showed catch-up growth in Ht during the first 2 years of life.[10] Moreover, in various studies the percentage of catch-up growth in Ht of preterm and ELBW SGA children ranged from 55% to 83% (with various definitions used for SGA).[10,15,16,24,25,58-60] Itabashi et al. found Ht catch-up rates (> -2 SDS) of 21% at 1 year and 74% at 3 and 5 years of age in a preterm cohort (32 weeks, born in 1980-2000).[58] Monset-Couchard et al. reported that the proportion of Ht catch-up (≥ -2 SD) was 78% at less than 3 years and 81% at 9 years of age in their ELBW SGA cohort (BW <1000g and <p10, born 1981-1995, n=166).[24]

The SGA children studied by Latal-Hajnal et al. (VLBW cohort born in 1983-1994, SGA defined as a BW <p10 for GA) had achieved catch-up growth (>p10) in Ht, Wt and OFC in 69.4%, 44.1%, and 65.9% respectively at 2 years of age. As for the AGA children catch-down growth was found in a substantial part of the children (9.9%, 28.9%, and 17.6% respectively).[15] Our data are partially in agreement with the results of Rieger et al. who reported limited catch-up growth in Wt (21% >p3) in children with a BW < 501g at 5 years of age, as for Ht and OFC the results were 63% and 26% respectively. However, the number of children studied was limited (n=19).[59]

In contrast, higher catch-up rates for all growth parameters were found by Finnstrom et al. The majority of their ELBW cohort (BW ≤1000g, GA 23 weeks, born in 1990-1992) achieved growth ≥ -2SDs at 36 months CA (Ht 83%, Wt 76%, OFC 90%).[60]

Postnatal growth patterns

Four different growth patterns were observed: SGA children who remained small versus those who showed catch-up growth, and AGA children with adequate

growth versus AGA children who displayed catch-down growth. However, no clear predictors could be found for the occurrence of the two different growth patterns of SGA children, other than a significantly higher BW, greater length and OFC at birth for SGA children who showed catch-up growth. Dusick et al. also reported that the incidence of growth failure in Ht, Wt and OFC increases as BW decreases.[13]Also no explanations for the occurrence of either adequate or catch-down growth of AGA children could be found. Nevertheless, we are of the opinion that our cohort (n=101) is most likely too small for identifying characteristics that affect the occurrence of these four different growth patterns.

Cognitive and motor developmental outcome

The majority of our ELBW cohort had a normal cognitive developmental outcome at 5.5 years of age, whereas their motor developmental outcome was poor.

Cognitive outcome did not differ significantly between the four growth patterns, although a trend was shown for a higher percentage of normal cognitive developmental outcome in SGA children with catch-up growth in Wt (84% versus 68.4%) compared to SGA children without catch-up growth. The same result was found for OFC (86.7% versus 68.4%) in SGA-OFC children vs AGA-OFC.

A significantly poorer motor developmental outcome was found in SGA children without catch-up growth in Wt/Ht compared to SGA children who did catch-up. The same holds true for AGA children who displayed catch-down growth in OFC compared to the AGA children with adequate growth. It seems to make sense that motor developmental outcome was adversely affected by postnatal growth, as motor performance depends on the abilities related to Ht, strength and Wt (and also OFC representing brain development).

Insufficient postnatal catch-up growth in preterm born infants has been significantly associated with an adverse neurodevelopmental outcome.[11,15,35] However, we failed to demonstrate this in our study.

Our findings are in agreement with those of Khan et al. and Latal-Hajnal et al.[29,15] The first group also reported no significant correlations between Wt and OFC SDS and IQ, nor correlations between changes in Wt and OFC and IQ in their cohort of preterm born children (GA <28 weeks, born 1991-1992, n=179). However, they found a poorer motor performance in children with significantly lower OFC SDS at 2 and 8 years of age.[29] The second group reported a significant association between Wt and Ht SDS and motor outcome (Psychomotor Index of the Bayley Scales of Infant Development-II) at 2 years of age. The poorest outcome was found in AGA children who displayed catch-down growth in Wt: their mental and motor functioning was significantly poorer than for AGA children with adequate growth, and even worse than for SGA children who failed to catch-up.[15]

However, Brandt et al. found no correlation between Ht catch-up growth and IQ at adult age (VLBW children, mean GA 33 weeks, born between 1967-1975),

whereas they did report a close correlation between OFC catch-up and IQ as well as neurologic development.[28]
Belfort et al. also reported OFC appropriate growth and weight gain during the first 12 months to be associated with better cognition at 6.5 years in a VLBW cohort (GA ≤ 37 weeks, born between 1985 and 1986).[61] The higher GA of the SGA VLBW children studied in both publications may have accounted for the better cognitive outcome results is as well. [28,61]

Background of postnatal growth failure
Qvigstad et al. showed that reduced growth achievement may result from cellular effects, dysregulation of growth processes after deleterious events or stress in the perinatal or postnatal period.[62] Also Marks et al. reported that poor catch-up growth, especially in preterm SGA infants, may be explained from complications associated with prematurity such as PDA, IRDS, BPD, NEC and sepsis.[63] Murphy et al. showed that postnatal steroids for BPD resulted in poor subsequent growth.[64] Lower maternal educational level was found to be associated with poor growth.[62,66,67] Furthermore, Fewtrell et al. showed that children with a BW < 1850g whose mothers had hypertension showed more catch-up growth and less stunting at 12 years compared to those whose mothers who were normotensive during pregancy.[65]
In our cohort, these maternal characteristics, perinatal events, and the use of hydrocortisone did not differ between the catch-up and no-catch-up SGA children. It is suggested that intrauterine growth restriction (IUGR) is a more important factor in determining childhood growth than neonatal complications.[23, 64]

To appreciate the presented results, some issues need to be addressed.
Missing data
Intra-uterine growth is known to be negatively affected by maternal smoking during pregnancy. Unfortunately data on maternal smoking behaviour were missing.
Ong et al. reported that infants of maternal smokers were lighter, shorter, and had smaller OFC, but were no different in Wt/Ht compared to non-smokers. However, the infants of smoking mothers showed complete compensatory postnatal catch-up growth in Wt, Ht and OFC during the first year of life, and by 12 months of age there was no longer a difference in growth parameters between smokers and non-smokers.[67] Even though maternal smoking data were not available, we feel that our postnatal growth results (from 15 months CA onward) are still valuable.
In our study the measurements of Ht, Wt, and OFC, and assessment of cognitive and motor development took place during regular follow-up visits. However, not all children did undergo the growth measurements and developmental assessments at each of the time points. We speculate about potential reasons for loss to follow-up in this cohort. One reason might be that the children were doing well and hence the parents did not feel the need for a visit to the follow-up clinic. Another reason might

be that children were having problems and an intervention program was already initiated by the local paediatrician. We compared the baseline characteristics, neonatal complications and cognitive and motor developmental outcome at earlier test ages between the non-missing and missing children, and no major differences were found (Table 6). In order to obtain all data for 101 children we decided to perform a single imputation missing value analysis.[56,57]

Growth curves

A limitation of this study, but actually of all studies evaluating growth parameters at birth, are the old reference charts used for calculating percentiles and SDS. Moreover, these charts are based on demographic populations that differ from the subjects studied. Thomas et al. showed that the American growth curves (Lubchenco and Usher and Mclean) are based on small samples, particularly at low GA, so that combined charts for males and females were composed.[69]

Increases in length and body mass index (BMI) have changed the Dutch population and life style changes and immigration since the 70's may have influenced BW of offspring of the Dutch population as well. The PRN recently published updated BW percentiles and SDS.[45,46] We used these PRN growth charts for determining BW SDS in our study population. Unfortunately, such updated growth curves are not yet available for length and OFC at birth, therefore we used the Usher and McLean growth curves (published in 1969).[47] Usage of the Usher and McLean growth norms for length and OFC at birth may have led to an overestimation of the SDS among males and a corresponding underestimation among females, as these norms are not gender specific.[69] However, Hack et al. also used the growth norms of Usher and Mclean, and performed additional analyses using sex-specific BW norms of Kramer et al. and Alexander et al., but no difference was found between the BW SDS calculated according to these three growth references.[66,70,71]

Other, more recent growth curves such as the Swedish Niklasson curves could not be used in our study population, because at present the version published in 1991 is only available in Growth analyser, and this version has a minimum GA of 28 weeks.[72]

One can argue whether length measurement at birth is reliable, as maximal stretching of the child is not recommended. Therefore, all studies which include length at birth can only present an approximation. But one should put effort in measuring length at birth, as Hokken-Koelega et al. reported birth length to be superior over BW in predicting catch-up growth in preterm SGA children.[10]

<u>Conclusions</u>

ELBW children with a BW ≤ 750g show significant deficits in Ht, Wt/Ht, Wt and OFC in early childhood. Growth in the first 2 years of life mostly determines the occurrence of catch-up growth, but after this time point the number of children with catch-up still increased, whereas some children showed temporarily catch-down

growth with subsequent catch-up.
Between birth and 5.5 years of age catch-up growth in Ht and Wt/Ht occurred in the majority of the SGA children with a BW ≤ 750g, but catch-up was less often seen for Wt and OFC. ELBW AGA children are likely to display catch-down growth especially in Wt and OFC. Lack of catch-up growth in Wt/Ht in SGA children as well as the occurrence of catch-down growth in OFC in AGA children are associated with the poorest motor developmental outcome. Cognitive outcome was not significantly associated with the different growth patterns of both AGA and SGA children.

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Table 5. Characteristics of missing versus non-missing IQ tests at 5.5 years of age.

	Missing n=40	Non-missing n=61	Missing vs non-missing
	n (%)	n (%)	p-value
Median maternal age (years) (min-max)	29.5 (21-43)	30 (17-45)	0.722
Median GA (weeks) (min-max)	27.8 (24.8-34.1)	28.0 (25.0-34.4)	0.690
Median birth weight (gram) (min-max)	660 (500-750)	690 (480-750)	0.365
Median birth length (cm) (min-max)	31.5 (27.0-37.0)	31.0 (21.0-35.8)	0.431
Median birth OFC (cm) (min-max)	23.0 (20.0-29.0)	23.5 (21.0-29.0)	0.790
Primiparae	34 (85.0)	44 (72.1)	0.152
Multiple birth	10 (25.0)	10 (16.4)	0.316
Male	15 (37.5)	30 (49.2)	0.308
Ethnicity (Caucasian)	37 (92.5)	56 (91.8)	1.000
SES			0.603
-high	9 (23.1)	12 (19.7)	
-average	26 (66.7)	38 (62.3)	
-low	4 (10.3)	11 (18.0)	
Maternal educational level			0.764
-high	4 (13.8)	8 (21.1)	
-average	13 (44.8)	15 (39.5)	
-low	12 (41.4)	15 (39.5)	
Prenatal steroids (GA <32 weeks)	31 (86.1)	50 (86.2)	1.000
Maternal hypertension	23 (57.5)	36 (59.0)	1.000
Caesarean delivery	31 (77.5)	52 (85.2)	0.426
5-min Apgar score <7	5 (12.5)	7 (11.5)	1.000
SGA	35 (85.7)	53 (86.9)	1.000
NICU admission > 28 days	34 (85.0)	53 (86.9)	1.000
Mechanical ventilation			0.726
-no	8 (20.0)	12 (19.7)	
-short < 2 weeks	12 (30.0)	17 (27.9)	
-intermediate	12 (30.0)	24 (39.3)	
-long	8 (20.0)	8 (13.1)	
Oxygen	36 (90.0)	56 (91.8)	0.737
IRDS			0.873
-no	18 (45.0)	25 (41.0)	
-grade I/II	10 (25.0)	18 (29.5)	
-grade III/ IV	12 (30.0)	18 (29.5)	
BPD	24 (60.0)	33 (54.1)	0.682
Hydrocortison treatment	19 (47.5)	31 (50.8)	0.839

	Missing n=40 n (%)	Non-missing n=61 n (%)	Missing vs non-missing p-value
Hypotension	26 (65.0)	37 (60.7)	0.681
PDA	16 (40.0)	18 (29.5)	0.290
Sepsis	22 (55.0)	40 (65.6)	0.304
NEC	6 (15.0)	3 (4.9)	0.150
PVL			0.295
-no	24 (60.0)	32 (52.5)	
-grade I	15 (37.5)	29 (47.5)	
-grade II	1 (2.5)	0	
IVH			0.526
-no	28 (70.0)	47 (77.0)	
-grade I/ II	11 (27.5)	11 (18.0)	
-grade III/IV	1 (2.5)	3 (4.9)	
Hyperbilirubinaemia	33 (82.5)	47 (77.0)	0.619
Hyperglycaemia	12 (30.0)	17 (27.9)	0.826
Hypoglycaemia	9 (22.5)	15 (24.6)	0.818
Hypothyroidism	2 (5.0)	2 (3.3)	1.000
Cognitive development 2yr CA			
-normal	31 (77.5)	44 (72.1)	0.864
-mildly delayed	2 (17.5)	14 (23.0)	
-severely delayed	2 (5.0)	3 (4.9)	
Cognitive development 3.5 years of age			
-normal	34 (85.0)	49 (80.3)	0.864
-mildly delayed	4 (10.0)	12 (19.7)	
-severely delayed	2 (5.0)	0	

SES: socio-economic status. *maternal educational level was available for n=67. GA: gestational age, OFC: occipital-frontal circumference. SGA: small for gestational age: height and/ or weight at birth <-2sds. NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PDA: patent ductus arteriosus, NEC: necrotizing enterocolitis, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage. Cognitive development: at 2 yr: Griffiths Mental Developmental Scales Developmental Quotient (DQ) Locomotor (LM) subscale excluded or Bayley Scales of Infant Development-II Mental Developmental Index, at 3.5 yr Griffiths Mental developmental Scales DQ-LM. Normal: Z-score ≥-1, mildly delayed: ≤-2 Z-score <-1, severely delayed: Z-score <-2, CA: corrected age.

Table 6. Characteristics of missing versus non-missing M-ABC data at 5.5 years of age.

	Missing n=31	Non-missing n=70	Missing vs non-missing
	n (%)	n (%)	p-value
Median maternal age (years) (min-max)	30 (19-43)	30 (17-45)	0.987
Median GA (weeks) (min-max)	28.0 (25-34.4)	27.8 (24.8-32.8)	0.702
Median birth weight (gram) (min-max)	680 (540-750)	670 (480-750)	0.482
Median birth length (cm) (min-max)	32.0 (28.0-35.5)	31.0 (21.0-37.0)	0.458
Median birth OFC (cm) (min-max)	23.2 (21.9-26.0)	23.2 (20.0-29.0)	0.347
Primiparae	25 (80.6)	53 (75.7)	0.621
Multiple birth	7 (22.6)	13 (18.6)	0.787
Male	11 (35.5)	34 (48.6)	0.280
Ethnicity (Caucasian)	28 (90.3)	65 (92.9)	0.698
SES			0.595
-high	8 (26.7)	13 (18.6)	
-average	17 (56.7)	47 (67.1)	
-low	5 (16.7)	10 (14.3)	
Maternal educational level			1.000
-high	4 (19.0)	8 (17.4)	
-average	9 (42.9)	19 (41.3)	
-low	8 (38.1)	19 (41.3)	
Prenatal steroids (GA <32 weeks)	21 (80.8)	60 (88.2)	0.339
Maternal hypertension	17 (54.8)	42 (60.0)	0.666
Caesarean delivery	26 (83.9)	57 (81.4)	0.790
5-min Apgar score <7	4 (12.9)	8 (11.4)	1.000
SGA	26 (83.9)	62 (88.6)	0.531
NICU admission > 28 days	24 (77.4)	63 (90.0)	0.120
Mechanical ventilation			
-no	9 (29.0)	11 (15.7)	0.482
-short < 2 weeks	8 (25.8)	21 (30.0)	
-intermediate	10 (32.3)	26 (37.1)	
-long	4 (12.9)	12 (17.1)	
Oxygen	26 (83.9)	66 (94.3)	0.128
IRDS			
-no	15 (48.4)	28 (40.0)	0.679
-grade I/II	7 (22.6)	21 (30.0)	
-grade III/ IV	9 (29.0)	21 (30.0)	
BPD	15 (48.4)	42 (60.0)	0.384
Hydrocortisone	12 (38.7)	38 (54.3)	0.196

	Missing n=31	Non-missing n=70	Missing vs non-missing
	n (%)	n (%)	p-value
Hypotension	16 (51.6)	47 (67.1)	0.182
PDA	8 (25.8)	26 (37.1)	0.362
Sepsis	17 (54.8)	45 (64.3)	0.384
NEC	4 (12.9)	5 (7.1)	0.451
PVL			0.174
-no	19 (61.3)	37 (52.9)	
-grade I	11 (35.5)	33 (47.1)	
-grade II	1 (3.2)	0	
IVH			0.915
-no	24 (77.4)	51 (72.9)	
-grade I/ II	6 (19.4)	16 (22.9)	
-grade III/IV	1 (3.2)	3 (4.3)	
Hyperbilirubinaemia	23 (74.2)	57 (81.4)	0.433
Hyperglycaemia	7 (22.6)	23 (31.4)	0.476
Hypoglycaemia	6 (19.4)	18 (25.7)	0.615
Hypothyroidism	1 (3.2)	3 (4.3)	1.000
CP	1 (3.2)	1 (1.4)	1.000
Motor development 2 yr CA			0.442
-normal	21 (67.7)	39 (56.5)	
-mildly delayed	6 (19.4)	22 (31.9)	
-severely delayed	4 (12.9)	8 (4.6)	
Motor development 3.5 yr			0.212
-normal	20 (64.5)	54 (77.1)	
-mildly delayed	9 (29.0)	15 (21.4)	
-severely delayed	2 (6.5)	1 (1.4)	

SES: socio-economic status. *maternal educational level was available for n=67. GA: gestational age, OFC: occipital-frontal circumference, SGA: small for gestational age: height and/ or weight at birth <-2sds. NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, CP: cerebral paresis. Motor development: at 2 yr Griffiths Mental Developmental Scales Locomotor and Eye-hand coordination subscales or Bayley Scales of Infant Development-II Psychomotor Developmental Index, at 3.5 yr Griffiths Mental developmental Scales Locomotor and Eye-hand coordination subscales. Normal: Z-score ≥ -1, mildly delayed: ≤-2 Z-score < -1, severely delayed: Z-score < -2, CA: corrected age.

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Summary and conclusions
General discussion

Summary and conclusions

In this thesis follow-up studies on extremely low birth weight (ELBW) infants with a BW ≤ 750g born between 1996 and 2005 in the Wilhelmina Children's Hospital in Utrecht in the Netherlands are presented. Attention was paid to maternal health issues, both before as well as during the present pregnancy, fetal and neonatal survival, neonatal morbidity, neurodevelopmental and motor developmental outcome at 2 years corrected age, 3.5 and 5.5 years of age, and postnatal growth.

In **chapter 1** we introduced the subject with preterm birth and intrauterine growth restriction (IUGR) as major causes for ELBW infants. Spontaneous preterm birth as well as IUGR originate from a number of demographic, maternal, fetal and placental factors. Important demographic factors are ethnicity, low socio-economic and educational status, low and high maternal age, single marital status, nutritional status, smoking, alcohol and drugs abuse. Furthermore pregnancy history; as there is an increased risk of recurrence of both preterm delivery and IUGR. Maternal medical conditions, such as a history of cervical cone biopsy or anomalies of the uterus, diabetes, hypertension, thyroid disease or asthma. Present pregnancy characteristics as cervical length, infections, vaginal bleeding and hypertension. Fetal factors include chromosomal or congenital disorders. Maldevelopment (absence of dilating remodelling of spiral endometrial arteries and fetal-placental angiogenesis) of the placenta is an important causative factor in IUGR, as well as structural abnormalities of the placenta (e.g. single umbilical artery, velamentous umbilical cord insertion, bilobate placenta, placental hemangiomas, infarcts or focal lesions), both are associated with problems in placental perfusion resulting in reduced fetal oxygenation. Furthermore, iatrogenic preterm delivery accounts for a substantial part of the preterm births as well, merely due to deteriorating maternal condition due to hypertensive disorders, pre-eclampsia, eclampsia or HELLP-syndrome combined with IUGR.

In **chapter 2** the assessments for evaluation of cognitive, behavioural and motor development used in this study are discussed in a chronological order. At 2 years corrected age (CA) the mental and motor development was assessed using either the Griffiths Mental Developmental Scales (GMDS) or the Bayley Scales of Infant Development-second-Dutch edition (BSID-II-NL). The GMDS was used in the majority of the children between 1996 and 2000, but from December 2000 onwards the BSID-II-NL was used. At 3.5 years of age the Griffiths Mental Developmental Scales for 2 to 8 years were used. At 5.5 years of age cognitive development was assessed by means of an intelligence test. This was either the Revisie Amsterdamse Kinder Intelligentie Test (RAKIT) or the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) or the Snijders-Oomen Nonverbal Intelligence Test-

Revised (SON-R). Behaviour was evaluated by means of the Child Behaviour Checklist (CBCL) and Teacher Report Form (TRF), which were completed by the parents and teachers respectively, prior to the intelligence test. The Movement Assessment Battery for Children (M-ABC-I or M-ABC-II) was used to assess the motor development at 5.5 years of age.

In **chapter 3** we described the obstetrical history and obstetrical complications of the maternal population who delivered an infant with a BW ≤ 750g. The total cohort (all different mothers who delivered an infant with a BW ≤ 750g between 1996-2005, n=261), cohort I (infants born between 1996-2000, n=145), cohort II (infants born between 2001-2005, n=116), appropriate for gestational age (AGA, BW ≥ p10, n=95) infants and small for gestational age (SGA, BW < p10, n=166) infants are separately described and compared.
Eighty-four percent of the multigravids (n=121) had a complicated obstetrical history: 46.3% miscarriage(s), 22.3% preterm delivery and 16.5% hypertensive disorders. In the index pregnancies (n=261) most prevalent complications were hypertensive disorders (52.1%), fetal distress (39.5%) and IUGR (32.6%). Hypertensive disorders were more prevalent both in cohort II (62.9% versus 43.4% in cohort I, *p*=0.002) and in SGA infants (58.4% versus 41.1% in AGA, *p*=0.007).
In the total cohort intra-uterine deaths occurred in 35.2%, merely due to placental insufficiency (59.8%) or termination of pregnancy because of a deteriorating maternal condition due to hypertensive disorders (23.9%). A large number of pregnancies were induced due to intra-uterine deaths or because of a deteriorating maternal condition due to hypertensive disorders. The caesarean section rate was 47.9% and a spontaneous vaginal delivery occurred in only 19.2%.
In conclusion, a high percentage of multiparous mothers had a complicated obstetrical history. The index pregnancy was in a high percentage complicated by hypertensive disorders and concomitant placental insufficiency. Due to this pathology the majority of infants with a BW ≤ 750g were growth restricted. An observation with important clinical implications for their follow-up.

In **chapter 4** we described the outcome of 179 live-born infants, of whom thirty-three (18.4%) infants died in the delivery room merely due to extreme prematurity. Survival and neonatal morbidity of the remaining 146/179 (81.6%) who were admitted to the Neonatal Intensive Care Unit (NICU) are presented. Cohort I (n=79) is compared with cohort II (n=67), and AGA infants (n=64) are compared with SGA infants (n=82). Of the total cohort 62.3% experienced infant respiratory distress syndrome (IRDS), 46.6% bronchopulmonary dysplasia (BPD), 50.7% septicaemia, 34.2% periventricular leukomalacia (PVL) grade I and 24.7% intraventricular haemorrhage (IVH) grade I/II. Severe intracranial lesions (PVL grade II and IVH grade III/IV) were not common (and PVL grade III and IV did not occur in our ELBW cohort).

In cohort I IRDS grade III/IV occurred significantly more often (p=0.042), whereas the prevalence of septicaemia and hyperbilirubinaemia was higher in cohort II (p=0.045 and p=0.001). AGA infants had a significantly shorter GA (p<0.001), and had significantly more often IRDS grade III/IV (p=0.015), mechanical ventilation (p=0.045) and patent ductus arteriosus (p=0.003) compared to SGA infants.
Overall survival of all live-born infants was 62% (111/179), whereas the survival rate of the NICU admissions was 76% (111/146). Survival of NICU admissions increased from 65.8% (cohort I) to 88.1% (cohort II, p=0.002). Survival of AGA and SGA infants did not differ significantly (73.4% and 78%, p=0.561). However, survival of AGA infants and SGA infants did increase with time (71.4% (AGA cohort I) to 75.9% (AGA cohort II), p=0.780 and 61.4% (SGA cohort I) to 97.4% (SGA cohort II), p< 0.001).
In conclusion, mortality of infants with a BW ≤ 750g is high, but decreased over time, especially in SGA infants. Considerable neonatal morbidity was present, especially in AGA infants, most likely due to their shorter gestational age.

In **chapter 5** the neurodevelopmental outcome (NDO) of the 101 children with a BW ≤ 750g who were assessed at 2 years CA is reported. The children were either assessed with the GMDS (n=49) or the BSID-II-NL (n=52). For NDO the GMDS developmental quotient without the locomotor (LM) subscale or the mental developmental index (MDI) of the BSID-II were used respectively. The outcome of the children assessed with the GMDS did not differ from the children assessed with the BSID-II-NL, and was therefore pooled. Cohort I (n=45) was compared with cohort II (n=56), and AGA children (n=45) were compared with SGA children (n=56).
Of the total cohort 74.3% of the children had a normal NDO at 2 years CA, 20.8% a mildly and 5% a severely delayed outcome. Although survival significantly increased over time (65.8% in cohort I to 88.1% in cohort II, p=0.002), significantly fewer children in cohort II (66.1% versus 84.4% in cohort I, p=0.042) as well as fewer SGA children (64.3% versus 86.7% of AGA children, p=0.012) had a normal NDO.
In conclusion, the large majority of children with a BW ≤ 750g had a normal NDO at 2 years CA. A normal NDO is more often seen in AGA children compared to SGA children. Increased survival of infants in cohort II coincided with an increased number of children with an impaired NDO at 2 years CA.

In **chapter 6** the NDO at 2 years CA, 3.5 and 5.5 years of age of 101 children with a BW ≤ 750g is presented. At 2 years CA the children were assessed by means of either the GMDS (LM subscale excluded, n=49) or the BSID-II-NL (MDI, n=51). At 3.5 years of age the GMDS (LM subscale excluded) were used and at 5.5 years of age the intelligence quotient (IQ) measured by either the RAKIT, WPPSI-III or SON-R intelligence test was used. Cohort I (n=45) was compared with cohort II (n=56), and AGA children (n=45) were compared with SGA children (n=56).
At 2, 3.5 and 5.5 years 74.3%, 82.2% and 76.2% had a normal NDO.

As shown in chapter 5, increased survival of children born between 2001-2005 coincided with a reduced number of children with a normal NDO at 2 years CA in cohort II compared to cohort I. The same was found for NDO at 3.5 years of age. However, at 5.5 years of age NDO and behaviour did not differ anymore between the two cohorts.
A normal NDO at 2 years CA positively predicted a normal NDO at 3.5 and 5.5 years in 92% and 84% respectively. Of the children with a mildly or severely delayed NDO at 2 years CA the majority showed an improved NDO at 3.5 (69.2%) and 5.5 years (65.4%) respectively.
In conclusion, NDO was normal in the large majority of children at 2 years CA, as already shown in chapter 5, but also at 3.5 and 5.5 years of age. A normal NDO at 2 years CA is a good predictor for normal outcome at 3.5 and 5.5 years, whereas a delayed NDO at 2 years CA is highly subject to change and therefore not reliable.
Nevertheless, the majority of the children with a mildly and severely delayed NDO at 2 years CA improved to a better NDO at 3.5 and 5.5 years of age.

In **chapter 7** the motor developmental outcome at 2 years CA, 3.5 and 5.5 years of age of 100 children with a BW ≤ 750g is presented. AGA children (n=44) were compared with SGA children (n=56). At 2 years CA 100 children were assessed by means of either the GMDS (LM and eye-hand coordination (EH) subscales, n=49) or the BSID-II-NL (psychomotor developmental index (PDI), n=51). The children assessed with the GMDS performed significantly better compared to the children who were assessed with the BSID-II-NL (p <0.001). However, the distribution of the GMDS and BSID-II-NL assessments was not significantly different between AGA (GMDS n=23, BSID-II-NL n=21) and SGA (GMDS n=26, BSID-II-NL n=30) children (p= 0.687).
At 3.5 years of age the GMDS (LM and EH subscales) were used and at 5.5 years of age the M-ABC- I or II (Total Impairment Score, TIS).
Cerebral palsy was present in only 2%. At 2, 3.5 and 5.5 years of age 60%, 74% and 42% had a normal motor developmental outcome. The stability of the motor outcome ranged from 46% to 53% between the test ages, and poor predictive values were found (C-statistics ranged between 0.57-0.63). So, classification of motor development at 2 years CA substantially differed from the classification at 3.5 and 5.5 years of age.
In conclusion, motor developmental outcome of children with a BW ≤ 750g is poor at 2, 3.5 and 5.5 years of age. Motor development was especially poor at 5.5 years of age. Our data suggest that 2 years CA is too early for diagnosing children with a delayed motor development, neither is it possible to reliably determine ELBW children with a normal motor development in early infancy.

In **chapter 8** the postnatal growth patterns and the association between different growth patterns and cognitive and motor developmental outcome at 5.5 years of age are shown. Standard deviation scores (SDS) of height (Ht), weight (Wt), weight for height (Wt/Ht) and occipital-frontal circumference (OFC) at birth, 15 months CA, 2 years CA, 3.5 and 5.5 years of age are presented. AGA children (defined as Ht or Wt at birth ≥-2 SDS, and OFC-AGA defined as OFC at birth ≥p10) are compared with SGA children (Ht and/or Wt at birth <-2 SDS, and OFC-SGA defined as OFC at birth <p10). At 5.5 years of age the IQ (measured by either the RAKIT, WPPSI-III or SON-R intelligence test) and the M-ABC-I or II (Total Impairment Score) were used for cognitive and motor developmental outcome, respectively.
Between birth and 5.5 years of age catch-up growth in Ht, Wt/Ht, Wt and OFC was seen in 72.7%, 79.5%, 56.8% and 44.1% respectively of the SGA children. Catch-up mostly occurred between birth and 2 years CA. For AGA children we found substantial catch-down growth for Ht (15.4%), Wt (30.8%) and OFC (18.2%). Cognitive and motor outcome was normal in respectively 76.2% and 41.6% of AGA and SGA children. While cognitive outcome did not differ between the children with different growth patterns, significantly more SGA children without catch-up growth in Wt/Ht had a severely delayed motor outcome compared to SGA children with catch-up (55.6% vs 22.9%, p=0.008). Also, significantly more AGA children with catch-down growth in OFC had a severely delayed motor outcome compared to AGA children with adequate growth (66.7% vs 11.1%, p=0.015).
In conclusion, between birth and 5.5 years of age catch-up growth in Ht and Wt/Ht occurred in the majority of the SGA children with a BW ≤ 750g, but was less often seen in Wt and OFC. ELBW AGA children are likely to display catch-down growth especially in Wt and OFC. Growth in the first 2 years of life mostly determines the occurrence of catch-up growth, but after this time point the number of children with catch-up still increased, whereas some children showed temporarily catch-down growth with subsequent catch-up. Lack of catch-up growth in Wt/Ht in SGA children as well as the occurrence of catch-down growth in OFC in AGA children are associated with the poorest motor developmental outcome. Cognitive outcome was not significantly associated with the different growth patterns of both AGA and SGA children.

Conclusions

- A high percentage of multiparous mothers who delivered an infant with a BW ≤ 750g had serious complications in their obstetrical history.
- The index pregnancy was largely complicated by hypertensive disorders and placental insufficiency, so the majority of the infants with a BW ≤ 750g are growth restricted.
- Mortality of infants with a BW ≤ 750g is considerable, but decreased over time.

The significantly higher BW, fewer respiratory problems and reduced requirement of

mechanical ventilation in cohort II may have accounted for this increased survival.
- Increased survival was especially shown in SGA infants, most likely due to their greater GA compared to AGA infants.
- Considerable neonatal morbidity was present, especially in AGA infants, most likely due to their significantly shorter GA.
- The majority of the children with a BW ≤ 750g had a normal neurodevelopmental outcome (NDO) at 2, 3.5 and 5.5 years of age.
- Increased survival of infants with a BW ≤ 750g coincided with an increased number of children with an impaired NDO at 2 years CA and 3.5 years of age, but this increase in impairment was no longer present at 5.5 years of age.
- SGA infants are especially at risk of an impaired NDO at 2 years CA.
- A normal NDO at 2 years CA is a good predictor for a normal outcome at 3.5 and 5.5 years of age. A delayed NDO at 2 years CA is highly subject to change and therefore not reliable. Nevertheless, the majority of the children with a mildly and severely delayed NDO at 2 years CA improved to a better NDO at 3.5 and 5.5 years of age.
- ELBW children ≤ 750g at birth are considerably at risk of motor developmental impairment in early infancy, especially at school-age. However, these children predominantly show clumsy and immature motor performance, which may improve during childhood, as cerebral palsy was present in only 2%.
- Classification of motor development at 2 years CA substantially differed from the classification at 3.5 and 5.5 years of age. Therefore, 2 years CA is too early for diagnosing children with a delayed motor development, neither is it possible to reliably determine ELBW children with a normal motor development in early infancy.
- Between birth and 5.5 years of age catch-up growth in height and weight for height occurred in the majority of the SGA children with a BW ≤ 750g, but was less often seen in weight and occipital-frontal circumference. ELBW AGA children are likely to display catch-down growth especially in weight and occipital-frontal circumference.
- Lack of catch-up growth in weight for height in SGA children as well as the occurrence of catch-down growth in occipital-frontal circumference in AGA children were associated with the poorest motor developmental outcome. Cognitive outcome was not significantly associated with the different growth patterns of both AGA and SGA children.

General discussion

Infants with a BW ≤ 750g account for only 0.26% of the total number of births born between 2000 and 2007 in the Netherlands.[1] Although these ELBW infants only comprise a minority of the general population, attention for these infants continues to increase since obstetrical and neonatal care is changing towards more active treatment of infants born at extremely low gestational ages. Also, the lack of curative treatment options for hypertensive disorders during pregnancy and concomitant placental insufficiency and IUGR will continue to result in the (iatrogenic) birth of ELBW infants. Despite improvements in perinatal and neonatal care, ELBW infants remain at risk of serious neonatal morbidity, neurodevelopmental and motor developmental impairment, behavioural disorders and impaired postnatal growth. Therefore, follow-up (studies) of ELBW infants remain of major importance.

Maternal population

The women who delivered an infant with a BW ≤ 750g are a high risk population with both a complicated obstetrical history and index pregnancies largely characterised by complications of placental origin: mainly placental insufficiency accompanied by severe hypertensive disorders, IUGR and intra-uterine deaths. A substantial part of the infants were delivered by caesarean section, largely due to fetal distress and severe maternal morbidity, whereas spontaneous preterm births occurred in a minority. Against this background we can question whether the birth of these infants can be prevented. Low dose of acetylsalicyl acid starting early in pregnancy in women with a history of pre-eclampsia and placental insufficiency has been shown to result in a minor reduction of this complication.[2] High dose of vitamin C and E to reduce the incidence of pre-eclampsia showed no effect.[3] A Cochrane review showed no beneficial effect on pregnancy outcome (maternal and perinatal mortality, major maternal and perinatal morbidity) in women with HELLP-syndrome experimentally treated with steroids.[4] Antihypertensive medication combined with magnesium sulphate (together with bethamethasone for acceleration of fetal lung maturation) remain nowadays the only treatment options. However, one knows that this treatment only results in a short improvement or a suppression of maternal morbidity and termination of the pregnancy remains the only curative treatment. Nevertheless, a neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is established by a Cochrane review. The authors found a significant reduction in the rate of cerebral palsy and reduced risk of gross motor dysfunction.[5]

Still, development of an improved and curative therapy for hypertensive disorders and placental insufficiency remains necessary in order to prevent the birth of infants with a BW ≤ 750g.

Survival and neonatal morbidity

The survival rate of our study population of live-born infants with a BW ≤ 750g was 62%, and 76% of our NICU admissions survived. Survival of infants admitted to the NICU, significantly improved over the two time periods studied. Possible explanations are the significantly higher mean BW, and fewer respiratory problems and reduced need for mechanical ventilation in cohort II.

Survival rates of infants with a BW ≤ 750g born between 1990 and 2005 reported by others ranged from 37.7% to 75.2%.[6-10] Poor survival of ELBW infants is strongly related to GA at birth: survival rates reported ranged from 47% to 95.5% for infants born between 24 weeks and < 30 weeks gestation (born between 1999-2007).[6,8,10,11] Others also reported significantly improved survival rates over time of infants with a BW below 750g.[12-14]

However, comparing other studies with our survival data is complicated, due to differences in inclusion criteria regarding the lower limit of gestation. Furthermore it is often not clearly stated whether antenatal death was accepted in infants with a very poor prognosis or whether some infants were not resuscitated in the delivery room for the same reason.

During NICU admission IRDS, BPD and septicaemia were common. One third was diagnosed with PVL grade I and one fourth with IVH grade I/II, whereas severe cerebral lesions (PVL grade II and IVH grade III/IV) were uncommon in our study population. Reports on infants with a BW ≤ 750g born between 1990 and 2002 presented similar rates of IRDS, BPD, septicaemia and IVH grade I/II, whereas the prevalence of IVH grade III/IV (12-24%) and cystic PVL (3-3.6%) was higher.[7,8,9,12]

In our study population survival of SGA and AGA infants was similar, but severe neonatal morbidity was more prevalent in AGA infants. Others reported SGA infants to be at increased risk for BPD, retinopathy of prematurity, NEC, IRDS, IVH and to have poorer survival rates compared to AGA infants.[15-17] The AGA infants of our study population were born at a significantly shorter mean GA and most likely therefore increased morbidity was found in our AGA infants, and no difference in survival was noted compared to SGA infants. Moreover, comparing our results of SGA and AGA infants with other studies, remains difficult due to differences in definition of SGA and varying obstetrical and perinatal policies as stated above.

Neurodevelopmental outcome at 2 years corrected age

Of the 101/111 (91%) children who were assessed at 2 years CA, the majority had a normal NDO, 20.8% a mildly and 5% a severely delayed outcome.

The severely delayed outcome reported by others ranged from 10.6% to 50%.[18-21]

The lower prevalence of severe developmental delay in our study population compared to other studies most likely results from the former clinical practice in the Netherlands, to provide intensive care from 25 weeks GA onward and to withdraw intensive care in infants with severe cardiorespiratory failure or a combination of

severe cardiorespiratory failure and severe cerebral lesions.
NDO at 2 years CA was significantly worse in cohort II in comparison with cohort I. The only possible explanation is the higher prevalence of hyperbilirubinaemia, as demographic and perinatal characteristics were not different and neonatal morbidity was even lower in cohort II.[22] Nevertheless, due to more active measures in obstetrical and neonatal care more severely compromised infants may be kept alive, which may have resulted in a protracted neonatal course with a higher prevalence of neurodevelopmental impairment.
Advances in developmental assessments resulted in the use of two different tests (GMDS and BSID-II-NL). From the literature and our own experience we know that some children perform better on the GMDS, because prolonged attention is required for the BSID-II-NL.[23] The use of the BSID-II-NL in the majority of cohort II could partly explain the poorer NDO. However, a comparison of the BSID-II-NL and GMDS Z-scores showed no significant differences.
Thus, in our population of ELBW infants, an increased survival rate was not accompanied by an improvement in NDO at 2 years CA.
The same is reported by others; increasing survival together with an increasing number of children with a MDI < 70.[24,25] However, a significantly decreased number of children with a MDI < 70 together with improved survival rates has also been found by others.[26,27]
Comparison of AGA and SGA children in our cohort showed a similar survival rate, but significantly more SGA children appeared to have an impaired NDO. Demographic and perinatal characteristics were not different and neonatal morbidity was even lower in the SGA cohort compared to AGA children. The most plausible explanation is that brain development was adversely affected in these severely growth retarded ELBW infants by chronic intra-uterine malnutrition.
Reports on NDO comparing AGA and SGA children show contradictory results, with either similar or poorer outcome for SGA children.[20,28-30] However, varying definitions of SGA and differences in neurodevelopmental assessment policy make it difficult to compare our data with other studies.

Neurodevelopmental outcome over time
The majority of the children had a normal NDO at 2, 3.5 and 5.5 years of age (74.3%, 82.2% and 76.2% respectively).
Literature presenting the data of a normal NDO at 2 years CA in ELBW children varies over a substantial range from 29.5% to 78.4%.[32-38] At 3.5 years of age, the few data found ranged from 44% to 77% in cohorts of ELBW and VLBW children.[38-42]
A normal NDO at 5 years of age in ELBW and preterm children reported by others ranged from 26% to 78%.[43-49] However, due to differences in the developmental assessments used and perinatal characteristics such as GA and neonatal morbidities of the cohorts studied comparison remains difficult.

At 3.5 years of age, as well as at 2 years CA, significantly fewer children in cohort II achieved a normal NDO. The same explanations as described above may account for this finding. However, at 3.5 years of age all children were assessed with the GMDS.
At 5.5 years of age, the NDO of cohort I and II did not differ anymore. Possible explanations could be the delayed maturation of extremely preterm born ELBW children. However, median GA was not different between cohort I and II and the median BW was even higher in cohort II. It is therefore more likely that a more correct estimation of NDO can be obtained at older ages, when the performance of these children is less affected by shyness and fear. Furthermore, usage of an actual intelligence test instead of a developmental test may have accounted for this finding as well.
The majority of the children with a normal NDO at 2 years CA also had a normal outcome at 3.5 and 5.5 years of age. The greater part of the children classified as mildly or severely delayed at 2 years CA had a better NDO at 3.5 and 5.5 years of age and only a few children got a more worse NDO.
Literature shows contradictory results with on the one hand studies also reporting earlier NDO assessments (at 2 or 3 years of age) to be predictive for NDO at school age,[48,50-54] and on the other hand studies who showed an increasing developmental delay between the assessment at earlier and later test ages.[55,56]
As shown by our data and the studies cited above, NDO of ELBW children is subject to change in about a quarter of studied cohorts in early childhood. However, we may conclude that children who are classified as normal in early infancy, most likely remain in this category, but 2 years CA is probably too early for a fixed diagnosis of a mildly or severely delayed development in ELBW infants. A possible explanation of an incorrectly estimated (i.e. worse) developmental prognosis of ELBW infants at earlier ages could be brain plasticity during childhood.[57]

Motor developmental outcome

We have demonstrated that ELBW children with a BW ≤ 750g are at considerable risk of motor developmental impairment. A substantial part of these children did not achieve a normal motor developmental outcome (40%, 26% and 58% respectively) at 2, 3.5 and 5.5 years of age.
Literature presenting the data of a normal motor developmental outcome at 2 years CA in extremely preterm born and ELBW children varies over a substantial range from 33% to 66.2%.[56-59] Normal motor developmental outcome at 3 years of age ranged from 30% to 67%.[60-63] A poor motor development at school-age is also reported by others and ranged from 45% to 64%.[66-70]
Classification of motor development at 2 years CA differed considerable from the classification at 3.5 and 5.5 years of age. Others also reported that only 53.3% of their VLBW cohort displayed a stable motor development through all test ages (5,

10, 18 months and 5.5 years of age). Of the children who showed unstable motor behaviour; 35.1% improved, 29.9% deteriorated and 35.1% fluctuated between the first and the last assessment.[68]
In our study, the number of ELBW children with a normal motor developmental outcome at 5.5 years of age is smaller compared to the previous test ages. Others reported that the prevalence of normal motor developmental outcome remained stable, decreased or increased over time.[62,64,70,71]
Differences in motor developmental outcome in early infancy and at school-age might
partially be explained by the fact that testing can be affected by lack of concentration, tiredness, lack of cooperation, shyness and even fear.[68,72] Furthermore, the overlap of motor difficulties with attention, cognition and behavioural problems complicates measurement of motor function. Standardized motor tests require the subject to understand the test, maintain concentration on the task and to inhibit other distracters, in addition to having the necessary motor and visuospatial skills. Consequently, poor motor performance can occur for a variety of reasons.[68,72-74]
Our data do suggest that 2 years CA is too early for diagnosing children with a delayed motor development, neither is it possible to reliably determine ELBW children with a normal motor development in early infancy. We therefore stress the importance of long-term follow-up of these ELBW children.

Postnatal growth patterns and cognitive and motor developmental outcome
Both SGA and AGA ELBW children with a BW ≤ 750g show significant deficits in height (Ht), weight for height (Wt/Ht), weight (Wt) and occipital-frontal circumference (OFC) in early childhood. Even at school-age the mean SDS of all anthropometric measurements was below zero. However, catch-up growth (between birth and 5.5 years of age) occurred mainly in Ht (72.7%) and Wt/Ht (79.5%), whereas catch-up growth in Wt and OFC was seen in respectively 56.8% and 44.1% of the SGA children. Catch-up growth occurred predominantly during the first 2 years, but after this time point the number of children with catch-up still increased, whereas some children showed temporarily catch-down growth with subsequent catch-up.
In various studies the percentage of catch-up growth in Ht of preterm and ELBW SGA children ranged from 55% to 83% (with various definitions used for SGA).[75-83]
In our cohort catch-down growth occurred particularly in Wt (30.8%, mostly during the first 2 years). The prevalence of catch-down growth in AGA children, varies in the literature from 2% to 28.9%.[76,78,80]
Four different growth patterns were observed: SGA children who remained small and SGA children who showed catch-up growth, and AGA children with adequate growth and AGA children who displayed catch-down growth. However, no clear predictors could be found for the occurrence of the two different growth patterns of SGA children, other than a significantly higher BW, greater length and OFC at birth for SGA children who showed catch-up growth. Although, we are of the opinion

that our cohort (n=101) is most likely too small for identifying characteristics that influence the occurrence of these different growth patterns.
The majority of our ELBW cohort had a normal cognitive developmental outcome at 5.5 years of age, whereas their motor developmental outcome was poor. Cognitive outcome did not differ significantly between the four growth patterns, although a trend was shown for a higher percentage of normal cognitive developmental outcome in SGA children with catch-up growth in Wt (84% versus 68.4%) compared to SGA children without catch-up growth. The same result was found for OFC (86.7% versus 68.4%) in SGA-OFC children vs AGA-OFC children.
Lack of catch-up growth in Wt/Ht and catch-down growth in OFC were associated with the poorest motor developmental outcome. A significantly poorer motor developmental outcome was found in SGA children without catch-up growth in Wt/Ht compared to SGA children who did catch-up. The same holds true for AGA children who displayed catch-down growth in OFC compared to the AGA children with adequate growth.
It seems to make sense that motor developmental outcome was adversely affected by postnatal growth, as motor performance depends on the abilities related to Ht, strength and Wt (and also OFC representing brain development).
Insufficient postnatal catch-up growth in preterm born infants has been significantly associated with an adverse neurodevelopmental outcome.[76,84,85] However, we failed to demonstrate this in our study.
Nevertheless, our findings are comparable to others who also reported no significant correlations between Wt and OFC SDS and IQ, but found a poorer motor performance in children with significantly lower OFC and Wt.[15,30] Furthermore, the poorest outcome was found in AGA children who displayed catch-down growth in Wt: their mental and motor functioning was significantly poorer than for AGA children with adequate growth, and even worse than for SGA children who failed to catch-up.[76]
In conclusion, both AGA and SGA ELBW children with a BW ≤ 750g are at risk of postnatal growth impairment in early childhood, catch-down growth as well as lack of catch-up growth are related to poor developmental outcome. Growth in the first 2 years of life mostly determines the occurrence of catch-up growth, but after this time point the number of children with catch-up still increased, whereas some children showed temporarily catch-down growth with subsequent catch-up. Therefore it is still questionable at which age it is recommended to initiate GH treatment in SGA children who show no catch-up growth.
Other studies have shown an increased prevalence of cardiovascular diseases and hypertension at older age in growth restricted infants.[86-89] Moreover, catch-up growth of SGA children further increases the risk of metabolic syndrome, insulin resistance and cardiovascular disorders. Therefore, complete and accurate follow-up of the physical and developmental status of preterm ELBW children, especially SGA, remains of major importance.

Strengths and limitations

There are some strengths and limitations related to the studies in this thesis.

A strength is that we included children born during a study period of 10 years in one hospital, resulting in a similar treatment policy for the whole cohort studied. Furthermore, we presented data on both two five year birth periods and a comparison of AGA and SGA children.

ELBW infants remain a hot topic since obstetrical and neonatal care is changing towards more active treatment of infants born at extremely low gestational ages, and also the inability to treat IUGR due to placental insufficiency and the unavailability of a curative treatment for hypertensive disorders during pregnancy, will continue to result in the (iatrogenic) birth of ELBW infants.

Despite improvements in perinatal and neonatal care, ELBW infants remain at risk of serious neonatal morbidity, neurodevelopmental and motor developmental impairment, behavioural disorders and impaired postnatal growth. Therefore, follow-up studies of ELBW infants remain of major importance.

The results of the studies described in this thesis may be used by obstetricians and neonatologists in order to make well balanced decisions regarding the care of ELBW infants and for counselling parents.

Advances in developmental assessments resulted in the use of two different tests (GMDS and BSID-II-NL) at 2 years CA, and at 5.5 years of age also two motor developmental tests were used, as the M-ABC-I has been replaced by the second version (M-ABC-II) in 2007. Altogether, in our study, seven different assessments (GMDS, BSID-II-NL, intelligence tests (RAKIT, WPPSI-III, SON-R), M-ABC-I and M-ABC-II) have been used for the assessment of development at three test ages (2 years CA, 3.5 and 5.5 years of age). There are differences in standardization, theoretical construct and the demands on performance capacities between the used instruments. Therefore, the developmental outcome may be either underestimated or overestimated due to the use of different assessments at different test ages. However, in order to compare developmental outcomes of different developmental assessments all scores were converted into Z-scores. Having to use these different tests is one of the limitations of the work presented in this thesis, but cannot be avoided, and already we are facing a change with BSID, having started to use the BSID-III rather than the BSID-II in 2008. Another limitation in the study on motor developmental outcome is that the GDMS is a test meant for screening motor performance, while the M-ABC is a pure motor performance test. Furthermore, the norms of the GMDS versions used are rather out-dated, which may have resulted in an overestimation of the developmental outcome of the children in our cohort assessed with the GMDS.

The old reference charts used for calculating percentiles and SDS is a limitation of all growth studies. Moreover, these charts are based on different demographic populations than the subjects studied (sometimes based on small samples,

particularly at low GA). The Dutch population as well as other populations have changed due to life style changes regarding smoking and diet and immigration, and are therefore not comparable to the subjects used to create the growth charts.
Finally we were faced with missing values for various subjects for different variables studied, however according to statistical regulations missing value analysis by single imputation was used.

Conclusions and recommendations for clinical practice

- Follow-up of infants with a BW ≤ 750g is extremely important because they are at risk for neonatal morbidity, cognitive and motor developmental impairment, behavioural problems and impaired postnatal growth.
-The majority of the ELBW children had a normal NDO in early childhood, however a delayed motor developmental outcome is found in the majority. These data are important for medical decision making and counselling.
- Long-term follow-up of ELBW infants is essential, as we have shown that increased survival of ELBW infants coincided with increased neurodevelopmental impairment at 2 years CA and 3.5 years of age.
- However, at 5.5 years of age there was no longer a difference in NDO between children from the two cohorts.
- A normal NDO at 2 years CA is a good predictor for normal outcome at 3.5 and 5.5 years, whereas a delayed NDO at 2 years CA is highly subject to change and therefore not reliable. Therefore, we suggest a change in emphasis of the ELBW children who definitely require long term follow-up: for the children who show a mildly or severely delayed NDO at the age of 2, long-term follow-up should be strongly recommended. For the children who show a normal NDO at 2 years CA, longer follow-up may be less essential, although still recommended, but could be done with greater intervals.
- Apart from NDO, ELBW children remain at risk for behavioural and socio-emotional impairment. Consequently, parents should be informed and realize that their ELBW child is at increased risk of behavioural and social problems, and therefore any support necessary should be easy accessible.
- ELBW infants are at risk of motor developmental impairment. However, motor developmental outcome cannot be diagnosed accurately in early infancy. Therefore, long-term follow-up of motor development in these ELBW infants is of major importance.
- Complete and accurate follow-up of the physical and developmental status of preterm ELBW children, especially SGA, remains of major importance, as these children remain at risk for growth impairment and neurocognitive developmental delay, as well as cardiovascular diseases and diabetes.
- Social consequences of remaining small should be considered, therefore if criteria are met, initiation of GH therapy should be considered and discussed with parents.

Although, since catch-up growth occurred predominantly in the first 2 years of life, but after this time point the number of children with catch-up still increased, whereas some children showed temporarily catch-down growth with subsequent catch-up, it is still questionable at what age GH treatment should be initiated in SGA children who show no catch-up growth.

Recommendations for further research

- To prevent the (iatrogenic) birth of ELBW infants development of an improved and curative therapy for hypertensive disorders and placental insufficiency remains necessary.
- Magnesium sulphate has been shown to result in a significant reduction in the rate of cerebral palsy and a reduced risk of gross motor dysfunction in preterm born children. However, beneficial effects of magnesium sulphate on motor or cognitive function in later childhood should be evaluated.[5]
- The development of other potential neuroprotective strategies such as magnesium sulphate is a challenging subject for further research.
- Further research in a larger study population, regarding short-term survival as well as development into childhood and adolescence is required as ELBW infants often grow into their deficits.
- Updated population based and sex specific growth curves for length and OFC at birth are urgently needed.
- To identify characteristics which determine whether SGA children will show catch-up growth and whether AGA children will display catch-down growth in a larger study population as these growth patterns are associated with cognitive and motor developmental outcome at school-age.
- Catch-up growth occurred predominantly in the first 2 years of life, but growth did not remain stable after this time point, it remains of interest to examine at what age GH treatment should be initiated in SGA children who show no catch-up growth at 2 years of age.
- We have shown that increased survival of infants with a BW ≤ 750g coincided with increased neurodevelopmental impairment at 2 years CA and 3.5 years of age, but not anymore at 5.5 years of age. Therefore, initiation of the new policy of a more active treatment of infants born at extremely low gestational ages must be accompanied by accurate long-term follow-up of these extremely preterm born and ELBW children.

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10

Nederlandse samenvatting
Summary in Dutch

Introductie

Dit proefschrift gaat over kinderen met een extreem laag geboortegewicht van 750 gram of minder, die tussen 1996 en 2005 in het Wilhelmina Kinderziekenhuis te Utrecht zijn geboren. De gezondheid van de moeders zowel voorafgaand aan als tijdens de zwangerschap wordt beschreven. De overleving en de ziekten die de pasgeborenen doormaken is nagegaan en de verstandelijke en motorische ontwikkeling op 2-, 3.5- en 5.5-jarige leeftijd en de groei van deze kinderen zijn bestudeerd.

Uit **hoofdstuk 1** blijkt dat vroeggeboorte en groeivertraging van het kind de belangrijkste oorzaken zijn voor het optreden van de geboorte van kinderen met een extreem laag geboortegewicht. Er zijn veel factoren die een rol spelen bij het optreden van vroeggeboorte en groeivertraging. Belangrijke moederlijke factoren zijn lage socio-econonomische status en een laag opleidingsniveau, oude of jonge leeftijd, een slechte voedingstoestand, roken, alcohol en drugsgebruik, suikerziekte, hoge bloeddruk en infecties etc. Chromosomale of aangeboren afwijkingen bij het kind gaan eveneens gepaard met zowel vroeggeboorte als groeivertraging. De placenta (moederkoek) is zeer belangrijk voor de groei van de baby, als deze niet goed is aangelegd of zich niet normaal ontwikkelt treedt er groeivertraging op. Hoge bloeddruk, zwangerschapsvergiftiging (een combinatie van te hoge bloeddruk en eiwitverlies via de urine) of HELLP- syndroom (Hemolysis Elevated Liver enzymes and Low Platelets, dit staat voor afbraak van rode bloedcellen, een gestoorde leverfunctie en een tekort aan bloedplaatjes) kunnen er toe leiden dat de zwangere ernstig ziek wordt. Beëindiging van de zwangerschap is de enige manier om de moeder te genezen, omdat de placenta een belangrijke rol speelt bij het ontstaan van deze ziekte. Omdat bij deze vroege zwangerschapsduur een normale bevalling voor het kind vaak ongewenst is, worden veel kinderen met een extreem laag geboortegewicht geboren via een keizersnede.

In **hoofdstuk 2** worden de verschillende testen die in dit onderzoek gebruikt zijn voor het meten van de verstandelijke, motorische en gedragsmatige ontwikkeling beschreven.
Op 2-jarige leeftijd zijn de kinderen ofwel met de Griffiths Mental Developmental Scales (GMDS) ofwel met de Bayley Scales of Infant Development-second-Dutch edition (BSID-II-NL) getest. De GMDS is bij het merendeel van de kinderen gebruikt in de periode tussen 1996 en 2000, maar vanaf december 2000 werd de BSID-II-NL gebruikt. Op 3.5-jarige leeftijd werd de GMDS voor kinderen in de leeftijd tussen 2 en 8 jaar gebruikt.
De GMDS bestaat uit de volgende 5 subschalen: locomotoriek, persoonlijk-sociaal, gehoor-spraak, oog- en hand coördinatie en performantie. Voor het testen van de verstandelijke ontwikkeling zijn de vier subschalen behalve de locomotoriek gebruikt.

Persoonlijk-sociaal meet bijvoorbeeld of een kind om dingen kan vragen. Gehoor-spraak test zowel het actief luisteren van het kind als de spraak- en taalvaardigheden door het kind bijvoorbeeld objecten aan te laten wijzen en te laten benoemen.
De oog- en hand coördinatie subschaal test bijvoorbeeld of het kind een toren met blokken kan bouwen. Performantie test het probleemoplossend vermogen van een kind en onderzoekt de manier waarop handvaardigheden worden toegepast in nieuwe situaties. Bijvoorbeeld het kind laten zoeken naar een object dat ingepakt is, of iets laten nabouwen. Voor het testen van de motorische ontwikkeling zijn twee subschalen gebruikt: locomotoriek (deze subschaal test bijvoorbeeld kruipen, zitten, staan en lopen) en de oog- en hand coördinatie subschaal.
De BSID-II-NL bestaat uit een mentale schaal en een motorische schaal. De mentale schaal verschaft een standaard score genaamd de Mental Development Index. Deze schaal evalueert een verscheidenheid aan leeftijdsafhankelijke vaardigheden; onder andere het oplossen van problemen, abstract denken en taalvaardigheden. De motorische schaal levert ook een standaard score genaamd de Psychomotor Development Index. Deze schaal test o.a. evenwicht, coördinatie en fijne vaardigheden van de handen en vingers.
Op 5.5-jarige leeftijd is de verstandelijke ontwikkeling met een intelligentietest gemeten. Dit was ofwel de Revisie Amsterdamse Kinder Intelligentie Test (RAKIT) of de Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) of de Snijders-Oomen Nonverbal Intelligence Test-Revised (SON-R). Het gedrag is geëvalueerd middels de Child Behaviour Checklist (CBCL) en de Teacher Report Form (TRF), deze werden respectievelijk ingevuld door de ouders en de leerkrachten. De CBCL en TRF zijn beide vragenlijsten die bestaan uit 100 vragen en stellingen over het gedrag van het kind.
De Movement Assessment Battery for Children (M-ABC-I of M-ABC-II) is gebruikt voor het testen van de motorische ontwikkeling op 5.5-jarige leeftijd. De M-ABC test drie rubrieken: handvaardigheid, balvaardigheid en evenwicht. Voorbeelden van het testen van handvaardigheid zijn: een kind kralen te laten rijgen in een zo kort mogelijke tijd en netjes tussen twee lijnen te laten tekenen. Balvaardigheid wordt bijvoorbeeld getest door het gooien en laten vangen van een pittenzakje. Evenwicht wordt getest door het kind zo lang mogelijk op 1 been te laten staan en voetje voor voetje (hiel–teen) over een lijn te laten lopen.

In **hoofdstuk 3** worden de complicaties van de voorgaande zwangerschap en de complicaties van de indexzwangerschap van de moeders die zijn bevallen van een kind met een geboortegewicht ≤ 750g beschreven. In totaal werden tussen 1996 en 2005 272 kinderen met een geboortegewicht ≤ 750g geboren. In dit hoofdstuk worden 261 moeders geanalyseerd: de moeders die meer dan een keer bevielen zijn eenmaal geteld en hetzelfde geldt voor de moeders die van een tweeling of drieling bevielen. Tussen 1996 en 2001 waren dit 145 moeders (cohort I) en tussen 2001

en 2005 waren dit 116 moeders (cohort II). Het totale cohort, cohort I en II worden beschreven en met elkaar vergeleken. Verder is de groep kinderen onderverdeeld in kinderen met een normaal gewicht voor de duur van de zwangerschap de zogenaamde 'appropriate for gestational age' (AGA) kinderen, dit waren er 95 en kinderen met een te laag gewicht voor de duur van de zwangerschap de 'small for gestational age' (SGA, geboortegewicht < p10, dit waren er 166). De AGA's worden vergeleken met de SGA's.
84% van de 121 vrouwen die al eerder zwanger waren geweest voordat zij bevielen van een kind met een geboortegewicht ≤ 750g hadden complicaties tijdens voorgaande zwangerschappen. Miskramen waren opgetreden in 46.3%, vroeggeboorte in 22.3%, hoge bloeddruk, zwangerschapsvergiftiging of HELLP-syndroom in 16.5%. De meest voorkomende complicaties tijdens de 261 zwangerschappen waaruit de kinderen met een geboortegewicht ≤ 750g werden geboren waren: hoge bloeddruk, zwangerschapsvergiftiging of HELLP-syndroom (52.1%), foetale nood, dat wil zeggen een foetus met dreigend zuurstofgebrek (39.5%) en groeivertraging (32.6%). Hoge bloeddruk, zwangerschapsvergiftiging of HELLP-syndroom kwamen significant meer voor in cohort II (62.9% versus 43.4% in cohort I) en meer bij moeders van SGA kinderen (58.4% versus 41.1% bij AGA).
In het hele cohort trad een intra-uteriene vruchtdood (dat wil zeggen het overlijden van de foetus in de baarmoeder) op in 35.2%, met name door het slecht functioneren van de placenta (59.8%) of door het beëindigen van de zwangerschap in verband met een ernstige verslechterende conditie van de zwangere ten gevolge van een hoge bloeddruk, zwangerschapsvergiftiging of HELLP-syndroom (23.9%). Een groot aantal van de bevallingen werd opgewekt omdat een intra-uteriene vruchtdood was opgetreden, of vanwege de verslechterende conditie van de zwangere vrouw ten gevolge van ernstige hoge bloeddruk. Het percentage keizersneden was 47.9% en slechts 19.2% van de kinderen werd via een spontane vaginale bevalling geboren.
Concluderend, een hoog percentage van de vrouwen die bevielen van een kind met een geboortegewicht ≤ 750g hadden ernstige complicaties tijdens voorgaande zwangerschappen. De indexzwangerschappen werden in een hoog percentage gecompliceerd door hoge bloeddruk, zwangerschapsvergiftiging of HELLP-syndroom en daarbij een slechte werking van de placenta. Hierdoor is er bij het grootste deel van de kinderen met een geboortegewicht ≤ 750g ook sprake van groeivertraging. Deze groeivertraging kan een afwijkende hersenontwikkeling tot gevolg hebben, en deze kinderen hebben een verhoogd risico op problemen in hun verstandelijke, gedragsmatige en motorische ontwikkeling. Daarom is follow-up van kinderen met een extreem laag geboortegewicht van groot belang.

In **hoofdstuk 4** hebben we de 179 levend geboren kinderen met een geboortegewicht ≤ 750g beschreven. Van deze kinderen overleden er 33 (18.4%) in de verloskamer, met name ten gevolge van extreme vroeggeboorte. Van de 146 (81.6%) op de

Neonatale Intensive Care Unit (NICU) opgenomen kinderen is de korte termijn follow-up beschreven.
Hierbij is cohort I (n=79) vergeleken met cohort II (n=67), en zijn AGA kinderen (n=64) vergeleken met SGA kinderen (n=82). Van het totale cohort ontwikkelde 62.3% infant respiratory distress syndrome (IRDS) en 46.6% bronchopulmonale dysplasie (BPD), dit zijn ernstige longproblemen waarvoor veelal langdurige beademing nodig is. 50.7% van de kinderen maakte een sepsis (bloedvergiftiging) door, 34.2% een periventriculaire leukomalacie (PVL) graad I, dit is een aandoening waarbij door vroeggeboorte milde afwijkingen in de witte stof van de hersenen zijn ontstaan en 24.7% een intraventriculaire bloeding (IVH) graad I/II, dit zijn bloedingen in de holtes van de hersenen die in de normale situatie hersenvocht bevatten. Ernstige hersenafwijkingen (zoals PVL graad II-IV en IVH graad III/IV) kwamen bijna niet voor in ons cohort.
De kinderen in cohort I ontwikkelden vaker longproblemen dan in cohort II, terwijl de kinderen in cohort II vergeleken met cohort I vaker een sepsis en vaker hyperbilirubinaemie (geelzucht) doormaakten. Bij AGA kinderen kwamen in vergelijking met SGA kinderen meer longproblemen voor en was vaker beademing nodig, ook bleef vaker de ductus arteriosus (het bloedvat dat de aorta met de longslagader verbindt) open. Normaal gesproken sluit dit bloedvat na de geboorte. Deze AGA kinderen werden bij een kortere zwangerschapsduur geboren in vergelijking met SGA kinderen, en maakten daardoor waarschijnlijk meer ziekten door.
De uiteindelijke overleving van alle levend geboren kinderen was 62% (111/179), terwijl de overleving van de kinderen die op de NICU werden opgenomen 76% (111/146) was. De overleving van de op de NICU opgenomen kinderen was in cohort I 65.8% en in cohort II 88.1%. Dit is een statisch significante toename. De overleving van AGA en SGA kinderen was niet verschillend (respectievelijk 73.4% en 78%). Echter, de overleving van zowel AGA als SGA kinderen nam toe tijdens de studieperiode van 71.4% (AGA cohort I) naar 75.9% (AGA cohort II), en van 61.4% (SGA cohort I) naar 97.4% (SGA cohort II).
Concluderend, sterfte van kinderen met een geboortegewicht ≤ 750g is aanzienlijk, maar werd in de loop van de studieperiode duidelijk minder; met name bij SGA kinderen. Tijdens de opname op de NICU werden veel kinderen ernstig ziek, vooral AGA kinderen, waarschijnlijk ten gevolge van hun korte zwangerschapsduur in vergelijking met SGA kinderen.

In **hoofdstuk 5** wordt de verstandelijke ontwikkeling op 2-jarige leeftijd van 101 kinderen met een geboortegewicht ≤ 750g beschreven. Deze kinderen zijn ofwel met de GMDS (n=49) of met de BSID-II-NL (n=52) getest. De verstandelijke uitkomst van de kinderen getest met de GMDS verschilde niet van de uitkomst van de kinderen getest met de BSID-II-NL, en daarom zijn de uitkomsten samengevoegd. Cohort I

(n=45) is vergeleken met cohort II (n=56), en AGA kinderen (n=45) zijn vergeleken met SGA kinderen (n=56).
Verreweg het grootste deel van het totale cohort (74.3%) had een normale verstandelijke ontwikkeling op 2-jarige leeftijd, 20.8% een mild vertraagde en 5% een ernstig vertraagde ontwikkeling. Ondanks de significante toename in overleving tijdens de studieperiode (van 65.8% in cohort I naar 88.1% in cohort II), hadden significant minder kinderen in cohort II (66.1% versus 84.4% in cohort I) een normale verstandelijke ontwikkeling op 2-jarige leeftijd.
SGA kinderen in het totale cohort hadden in vergelijking met AGA kinderen ook minder vaak een normale verstandelijke ontwikkeling op 2-jarige leeftijd (64.3% van de SGA kinderen versus 86.7% van de AGA kinderen).
Concluderend, de meerderheid van de kinderen met een geboortegewicht ≤ 750g had een normale verstandelijke ontwikkeling op 2-jarige leeftijd. Een normale verstandelijke ontwikkeling werd vaker gezien bij AGA kinderen dan bij SGA kinderen. De toegenomen overleving van kinderen in cohort II is geassocieerd met een toegenomen aantal kinderen met een vertraagde verstandelijke ontwikkeling op 2-jarige leeftijd. Tussen cohort I en II werden geen verschillen gevonden die een minder goede verstandelijke ontwikkeling van kinderen in cohort II kunnen verklaren. Misschien werden door de meer actieve behandeling van te vroeg geboren kinderen met een extreem laag geboortegewicht in de tweede periode van de studie, toch meer ernstig zieke kinderen in leven gehouden, met als gevolg een minder goede verstandelijke ontwikkeling op 2-jarige leeftijd.

In **hoofdstuk 6** is de verstandelijke ontwikkeling op 2-, 3.5- en 5.5-jarige leeftijd van 101 kinderen met een geboortegewicht ≤ 750g beschreven. Op 2-jarige leeftijd zijn de kinderen ofwel met de GMDS (n=49) ofwel met de BSID-II-NL (n=51) getest. Op 3.5-jarige leeftijd is de GMDS gebruikt. Op 5.5-jarige leeftijd is het intelligentie quotient (IQ) gemeten met ofwel de RAKIT, WPPSI-III of de SON-R intelligentietest. Cohort I (n=45) is vergeleken met cohort II (n=56), en AGA kinderen (n=45) zijn vergeleken met SGA kinderen (n=56).
Op 2-, 3.5- en 5.5-jarige leeftijd had respectievelijk 74.3%, 82.2% en 76.2% van alle kinderen een normale verstandelijke ontwikkeling. Zoals beschreven in hoofdstuk 5, is de toename in overleving van kinderen geboren tussen 2001 en 2005 in vergelijking met de periode 1996-2001, geassocieerd met een afname van het aantal kinderen met een normale verstandelijke ontwikkeling op 2-jarige leeftijd. Dezelfde bevindingen werden gedaan bij de verstandelijke ontwikkeling op 3.5-jarige leeftijd. Echter, op 5.5-jarige leeftijd was er geen verschil meer in de verstandelijke en gedragsmatige ontwikkeling tussen de kinderen geboren in de twee perioden. De reden hiervoor zou kunnen zijn dat er op 5.5-jarige gebruik is gemaakt van een intelligentietest, in tegenstelling tot de ontwikkelingstesten die op 2- en 3.5-jarige leeftijd zijn gebruikt. Het is ook mogelijk dat de scores op 2- en 3.5-jarige leeftijd

meer beïnvloed zijn door verlegenheid van de kinderen en mogelijke angst voor de onderzoeker, en dat kinderen op 5.5-jarige leeftijd makkelijker een test ondergaan en dit een betrouwbaardere schatting van de verstandelijke ontwikkeling oplevert. Een andere mogelijk is, dat de kinderen in de loop van de tijd een positieve ontwikkeling in hun verstandelijk functioneren hebben doorgemaakt door rijping van hun hersenfuncties, of positieve effecten van hun omgeving zoals de peuterspeelzaal, kinderdagverblijf en school.
Een normale verstandelijke ontwikkeling op 2-jarige leeftijd voorspelde een normale verstandelijke ontwikkeling op 3.5- en 5.5-jarige leeftijd in respectievelijk 92% en 84%. De meerderheid van de kinderen met een mild vertraagde of ernstig vertraagde ontwikkeling op 2-jarige leeftijd had een betere verstandelijke ontwikkeling op 3.5- (69.2%) en 5.5-jarige leeftijd (65.4%).
Concluderend, de verstandelijke ontwikkeling was normaal in de meerderheid van de kinderen met een geboortegewicht ≤ 750g op 2-, 3.5- en 5.5-jarige leeftijd. Een normale verstandelijke ontwikkeling op 2-jarige leeftijd voorspelt in hoge mate een normale ontwikkeling op 3.5- en 5.5-jarige leeftijd. Een vertraagde verstandelijke ontwikkeling op 2-jarige leeftijd is nog erg veranderlijk en daarom niet betrouwbaar om de ontwikkeling op latere leeftijd te voorspellen. De meerderheid van de kinderen met een mild of ernstig vertraagde ontwikkeling op 2-jarige leeftijd had een betere verstandelijke ontwikkeling op 3.5- en 5.5-jarige leeftijd.

In **hoofdstuk 7** wordt de motorische ontwikkeling op 2-, 3.5- en 5.5-jarige leeftijd van 100 kinderen met een geboortegewicht ≤ 750g geanalyseerd. AGA kinderen (n=44) werden vergeleken met SGA kinderen (n=56). Op 2-jarige leeftijd zijn de 100 kinderen getest met ofwel de GMDS (n=49) of de BSID-II-NL (n=51). De kinderen getest met de GMDS scoorden significant beter in vergelijking met de kinderen die met de BSID-II-NL werden getest. De verdeling van de GMDS en BSID-II-NL testen was niet significant verschillend tussen de AGA (GMDS n=23, BSID-II-NL n=21) en SGA (GMDS n=26, BSID-II-NL n=30) kinderen.
Op 3.5-jarige leeftijd werd de GMDS gebruikt en op 5.5-jarige leeftijd de M-ABC- I of II (Total Impairment Score).
Cerebrale parese ofwel hersenverlamming (een stoornis die wordt veroorzaakt door schade aan de hersenen voor, tijdens of na geboorte, die kan resulteren in een vorm van spasticiteit, minder goede coördinatie en andere motorische vaardigheden) kwam slechts voor in 2%. Op 2-, 3.5- en 5.5-jarige leeftijd had respectievelijk 60%, 74% en 42% van de kinderen een normale motorische ontwikkeling. De classificatie van de motorische ontwikkeling op 2-jarige leeftijd verschilde substantieel van de classificatie op 3.5- en 5.5-jarige leeftijd.
Concluderend, de motorische ontwikkeling van kinderen met een geboortegewicht ≤ 750g is sterk achtergebleven op 2-, 3.5- en 5.5-jarige leeftijd. De motorische ontwikkeling viel met name buiten de norm op 5.5-jarige leeftijd. Onze data laten

zien dat de leeftijd van 2 jaar te jong is voor het diagnosticeren van een vertraagde motorische ontwikkeling. Ook is het op deze leeftijd niet mogelijk betrouwbaar te bepalen welke kinderen later een normale motorische ontwikkeling zullen hebben.

In **hoofdstuk 8** komen de groeipatronen van de kinderen met een geboortegewicht ≤ 750g en de associatie tussen de verschillende groeipatronen en de verstandelijke en motorische ontwikkeling op 5.5-jarige leeftijd aan de orde. Lengte, gewicht en hoofdomtrek bij de geboorte, op 15 maanden, 2-, 3.5- en 5.5-jarige leeftijd worden beschreven. AGA kinderen (gedefinieerd als lengte of gewicht bij de geboorte ≥ -2 SDS (de standaard deviatie score (SDS) geeft aan hoeveel een individuele score van het gemiddelde (gedefinieerd als 0) afwijkt), en hoofdomtrek-AGA (gedefinieerd als hoofdomtrek bij de geboorte ≥p10) worden vergeleken met SGA kinderen (lengte en/of gewicht bij de geboorte <-2 SDS, en hoofdomtrek-SGA gedefinieerd als hoofdomtrek bij de geboorte <p10). Op 5.5-jarige leeftijd werd de verstandelijke ontwikkeling met behulp van een IQ test gemeten, dit was ofwel de RAKIT, WPPSI-III of SON-R intelligentietest. De M-ABC-I of II (Total Impairment Score) werd gebruikt voor de motorische ontwikkelingsuitkomst op 5.5-jarige leeftijd.
Tussen de geboorte en 5.5-jarige leeftijd trad inhaalgroei (gedefinieerd als een toename van de groei tussen twee meetmomenten die classificaties overschrijden: <-2 SDS naar ≥ -2 SDS of <p10 naar ≥p10) op in lengte, gewicht naar lengte, gewicht en hoofdomtrek in respectievelijk 72.7%, 79.5%, 56.8% en 44.1% van de SGA kinderen. Inhaalgroei vond vooral plaats tussen de geboorte en 2-jarige leeftijd. Voor AGA kinderen vonden we substantiële catch-down groei (gedefinieerd als een afname van de groei tussen twee meetmomenten die classificaties overschrijden) in lengte (15.4%), gewicht (30.8%) en hoofdomtrek (18.2%). De verstandelijke en motorische ontwikkeling was normaal in respectievelijk 76.2% en 41.6% van de AGA en SGA kinderen. Terwijl de verstandelijke ontwikkeling niet verschilde tussen kinderen met verschillende groeipatronen, hadden significant meer SGA kinderen zonder inhaalgroei in gewicht naar lengte een ernstig vertraagde motorische ontwikkeling vergeleken met SGA kinderen die wel inhaalgroei vertoonden (55.6% versus 22.9%). Een ernstig vertraagde motorische ontwikkeling werd ook significant vaker gezien in AGA kinderen met catch-down groei in hoofdomtrek in vergelijking met AGA kinderen die adequate groei van de hoofdomtrek vertoonden (66.7% versus 11.1%).
Concluderend, de meerderheid van de SGA kinderen met een geboortegewicht ≤ 750g liet inhaalgroei in lengte en gewicht naar lengte zien tussen de geboorte en 5.5-jarige leeftijd, maar dit was minder vaak aanwezig in de groei in gewicht en in hoofdomtrek. AGA kinderen ontwikkelden met name catch-down groei in gewicht en hoofdomtrek. De groei in de eerste 2 jaar is voornamelijk bepalend voor het optreden van inhaalgroei, maar ook na deze leeftijd neemt het aantal kinderen met inhaalgroei nog toe, terwijl sommige kinderen tijdelijk catch-down groei laten zien

en vervolgens opnieuw inhaalgroei laten zien. Het ontbreken van inhaalgroei in gewicht naar lengte in SGA kinderen, even als het optreden van de catch-down groei in hoofdomtrek in AGA kinderen is geassocieerd met het achterblijven van de motorische ontwikkeling. De verstandelijke ontwikkeling was niet geassocieerd met de verschillende groeipatronen van zowel AGA als SGA kinderen.

Belangrijkste conclusies van dit proefschrift

- Een hoog percentage van de vrouwen die bevielen van een kind met een geboortegewicht ≤ 750g hadden ernstige complicaties tijdens voorgaande zwangerschappen.
- De indexzwangerschappen werden in een hoog percentage gecompliceerd door hoge bloeddruk, zwangerschapsvergiftiging of HELLP-syndroom en daarbij een slechte werking van de placenta, hierdoor is in de meerderheid van de kinderen met een geboortegewicht ≤ 750g groeivertraging opgetreden.
- De sterfte van kinderen met een geboortegewicht ≤ 750g is aanzienlijk, maar neemt duidelijk af tijdens de studieperiode. Het significant hoger geboortegewicht, minder longproblemen en de verminderde behoefte tot beademing van kinderen in cohort II zouden verantwoordelijk kunnen zijn voor deze toename in overleving.
- De toename in overleving werd vooral gezien in SGA kinderen, meest waarschijnlijk ten gevolge van hun langere zwangerschapsduur.
- Tijdens de NICU opname waren veel kinderen ernstig ziek, vooral AGA kinderen waarschijnlijk ten gevolge van hun kortere zwangerschapsduur.
- De meerderheid van de kinderen met een geboortegewicht ≤ 750g had een normale verstandelijke ontwikkeling op 2-, 3.5- en 5.5-jarige leeftijd.
- De toename in overleving van kinderen met een geboortegewicht ≤ 750g was geassocieerd met een toename in het aantal kinderen met een vertraagde verstandelijke ontwikkeling op 2- en 3.5-jarige leeftijd, maar deze toename in het aantal kinderen met een vertraagde ontwikkeling was niet meer aanwezig op 5.5-jarige leeftijd.
- SGA kinderen hebben met name een risico op een vertraagde verstandelijke ontwikkeling op 2-jarige leeftijd.
- Een normale verstandelijke ontwikkeling op 2-jarige leeftijd voorspelt in hoge mate een normale ontwikkeling op 3.5- en 5.5-jarige leeftijd. Een vertraagde verstandelijke ontwikkeling op 2-jarige leeftijd kan nog alleszins veranderen en is daarom niet goed voorspellend voor de verstandelijke ontwikkeling op latere leeftijd. De meerderheid van de kinderen met een mild of ernstig vertraagde verstandelijke ontwikkeling op 2-jarige leeftijd hadden een betere verstandelijke ontwikkeling op 3.5- en 5.5-jarige leeftijd.
- Kinderen met een geboortegewicht ≤ 750g hebben een risico op een vertraagde motorische ontwikkeling, met name op de schoolgaande leeftijd. Het motorisch functioneren van deze kinderen is met name onhandig en onrijp, en dit kan in de

loop van de tijd nog verbeteren.
- Classificatie van de motorische ontwikkeling op 2-jarige leeftijd verschilde substantieel van de classificatie op 3.5- en 5.5-jarige leeftijd. Daarom is de leeftijd van 2 jaar ongeschikt voor het diagnosticeren van een blijvend vertraagde motorische ontwikkeling, ook is het op deze leeftijd niet mogelijk betrouwbaar vast te stellen welke kinderen later een normale motorische ontwikkeling zullen hebben.
- Tussen de geboorte en 5.5-jarige leeftijd trad inhaalgroei in lengte en gewicht naar lengte op in de meerderheid van de SGA kinderen met een geboortegewicht ≤ 750g, maar dit was minder vaak aanwezig bij de groei in gewicht en hoofdomtrek. AGA kinderen ontwikkelden met name catch-down groei in gewicht en hoofdomtrek.
- Het ontbreken van inhaalgroei in gewicht naar lengte bij SGA kinderen, evenals het optreden van de catch-down groei in hoofdomtrek bij AGA kinderen is geassocieerd met het achterblijven van de motorische ontwikkeling. De verstandelijke ontwikkeling was niet geassocieerd met de verschillende groeipatronen van noch de AGA noch de SGA kinderen.
- Follow-up van kinderen met een geboortegewicht ≤ 750g is zeer belangrijk, omdat deze kinderen naast de ernstige korte termijn problemen een verhoogd risico hebben op latere ontwikkelingsproblemen van zowel verstandelijke, als gedragsmatige als motorische aard en groeistoornissen.

Appendices

Table 1. Cause of death of delivery room deaths.

	Total cohort n=33	Cohort I n=15	Cohort II n=18	Cohort I vs II	AGA n=17	SGA n=16	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
No active resuscitation in view of extreme prematurity	18 (54.5)	7 (46.7)	11 (61.1)	0.671	10 (58.8)	8 (50.0)	**0.001***
Severe intra-uterine infection	7 (21.2)	3 (20.0)	4 (22.2)		7 (41.2)	0	
Termination of pregnancy due to deteriorating maternal condition*	4 (12.1)	3 (20.0)	1 (5.6)		0	4 (25.0)	
Placental insufficiency	3 (9.1)	1 (6.7)	2 (11.2)		0	3 (18.8)	
Twin-to-twin transfusion syndrome	1 (3.0))	1 (6.7)	0		0	1 (6.3)	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age: birth weight (BW) ≥p10, SGA: small for GA: BW <p10. Maternal condition: severe preeclampsia, eclampsia or HELLP syndrome. * indicates $p < 0.05$.

Table 2. Cause of death of NICU deaths.

	Total cohort n=35	Cohort I n=27	Cohort II n=8	Cohort I vs II	AGA n=81	SGA n=98	AGA vs SGA
	n (%)	n (%)	n (%)	p-value	n (%)	n (%)	p-value
Discontinuation of IC because of severe cardiorespiratory failure	23 (65.7)	20 (74.1)	3 (37.5)	**0.043***	9 (52.9)	14 (77.8)	0.122
Discontinuation of IC because of severe cardiorespiratory failure and severe cerebral lesions	7 (20.0)	3 (11.1)	4 (50.0)		6 (35.3)	1 (5.6)	
Discontinuation of IC because severe cerebral lesions	5 (14.3)	4 (14.8)	1 (12.5)		2 (11.8)	3 (16.7)	

Total cohort: infants born in 1996-2005, cohort I: 1996-2000, cohort II: 2001-2005, AGA: appropriate for gestational age: birth weight (BW) ≥p10, SGA: small for GA age: BW <p10, NICU: neonatal intensive care unit, IC: intensive care. * indicates $p < 0.05$.

Table 3. Walking age of AGA and SGA children.

	Total cohort n=95	AGA n=41	SGA n=54	AGA vs SGA
	n (%)	n (%)	n (%)	p-value
Mean CA (months)	16.26	16.2	16.45	0.801
(SD, min~max)	(3.1, 9-23.5)	(3.3, 9.0~23.0)	(3.0, 11.25~23.5)	
Mean UCA (months)	19.1	19.1	19.0	0.760
(SD, min~max)	(3.1, 11.9~26.0)	(3.4, 11.9~26.0)	(3.0, 13.53~25.6)	

Total cohort: appropriate for gestational age (AGA) and small for gestational age (SGA) children. CA: corrected age, UCA: uncorrected age. SD: standard deviation, min: minimum, max: maximum.

Table 4a. Classification of motor developmental outcome at 2 and 5.5 years of age in 49 ELBW children assessed with the GMDS at 2 years CA.

Motor development classification at 2 y	Motor development classification at 5.5 y, n (%)			Total, n (%)
	Normal	Mildly delayed	Severely delayed	
Normal	17 (40.5) [a]	12 (28.6) [c]	13 (31.0) [c]	42 (85.7)
Mildly delayed	3 (60.0) [b]	0	2 (40.0) [c]	5 (10.2)
Severely delayed	0	0	2 (100) [a]	2 (4.1)
Total	20 (40.8)	12 (24.5)	17 (34.7)	49 (100)

Percentages are row percentages, except for the totals for 2 years, which are column percentages. [a] unchanged, [b] improved, [c] deteriorated. For missing values of motor outcome at 5.5 years of age single imputation was used.

Table 4b. Classification of motor developmental outcome at 2 and 5.5 years of age in 51 ELBW children assessed with the BSID-II at 2 years CA.

Motor development classification at 2 y	Motor development classification at 5.5 y, n (%)			Total, n (%)
	Normal	Mildly delayed	Severely delayed	
Normal	12 (66.7) [a]	4 (22.2) [c]	2 (11.1) [c]	18 (35.3)
Mildly delayed	9 (39.1) [b]	9 (39.1) [a]	5 (21.7) [c]	23 (45.1)
Severely delayed	1 (10.0) [b]	3 (30.0) [b]	6 (60.0) [a]	10 (19.6)
Total	22 (43.1)	16 (31.4)	13 (25.5)	51 (100)

Percentages are row percentages, except for the totals for 2 years, which are column percentages. [a] unchanged, [b] improved, [c] deteriorated. For missing values of motor outcome at 5.5 years of age single imputation was used.

Table 5. Predictive value of motor developmental outcome between either GMDS or the BSID at 2 years CA and the M-ABC at 5.5 years of age.

	Sensitivity	Specificity	PPV	NPV
	%	%	%	%
GMDS 2yr for TIS 5.5 yr	85%	13.8%	40.5%	57.1%
BSID 2yr for TIS 5.5 yr	54.5%	79.3%	66.7%	69.7%

GMDS: LM+EH, BSID: PDI. PPV: positive predictive value, NPV: negative predictive value.

Table 6. Motor developmental outcome at 2 years CA and 3.5 years of age of right and left-handed ELBW children.

	Total n=77	Right-handed n=57	Left-handed n=19	Ambidexter n=1	Right vs left-handed
	n (%)	n (%)	n (%)	n (%)	p-value
2 yr CA					
Normal	48 (62.3)	35 (61.4)	12 (63.2)	1 (100)	0.833
Mildly delayed	21 (27.3)	15 (26.3)	6 (31.6)	0	
Severely delayed	8 (10.4)	7 (12.3)	1 (5.3)	0	
3.5 yr UCA					
Normal	57 (74.0)	41 (71.9)	15 (78.9)	1 (100)	0.073
Mildly delayed	18 (23.4)	16 (28.1)	2 (10.5)	0	
Severely delayed	2 (2.6)	0	2 (10.5)	0	

Total cohort: handedness available. Motor outcome: at 2 year: Griffiths Mental Development Scales (GMDS), subscale locomotor (LM) + subscale eye-hand coordination (EH) or Bayley Scales of Infant Development-II, motor scale. 3.5 year: GMDS LM + EH. 5.5 year: Movement-ABC Total Impairment Score. CA: corrected age, Outcome: normal: Z-score ≥-1, mildly delayed: -2 ≤ Z-score < -1, severely delayed: Z-score < -2. For missing values of motor outcome at 3.5 and 5.5 years single imputation was used.

Table 7a. Height and weight at 2 years CA and 3.5 years of age.

	3.5 years of age, n (%)	
2 years CA	<p10	≥ p10
Height		
<p10	51 (86.4)	8 (13.6)
≥ p10	28 (68.3)	13 (31.7)
Weight		
<p10	62 (89.9)	7 (10.1)
≥ p10	8 25.8)	23 (74.2)

CA: corrected age.

Table 7b. Height and weight at 3.5 years of age of AGA and SGA children.

	3.5 years of age, n (%)	
	<p10	≥ p10
Height		
SGA	41 (73.2)	15 (26.8)
AGA	23 (52.3)	21 (47.7)
Weight		
SGA	44 (78.6)	12 (21.4)
AGA	26 (59.1)	18 (40.9)

AGA: appropriate for gestational age: birth weight (BW) ≥p10, SGA: small for GA: BW <p10.

Table 8a. Differing perinatal characteristics and neonatal morbidity between SGA children without catch-up growth and SGA with catch-up in height between birth and 5.5 years of age.

	SGA no catch-up	SGA catch-up	No catch-up vs catch-up
	n=24	n=64	p-value
Median GA (weeks) (min~max)	28.8 (25.7~34.4)	28.0 (24.8~34.1)	0.088
Median BW (gram) (min~max)	622 (480~750)	685 (500~750)	**0.007**
Median birth length (cm) (min~max)	31.0 (21.0~35.0)	31.0 (28.0~35.0)	**0.033**
Median birth OFC (cm) (min~max)	23.0 (21.0~27.0)	23.5 (20.0~26.0)	**0.047**
Ethnicity (Caucasian)	21 (87.5)	60 (93.8)	0.385
Male	9 (37.5)	30 (46.9)	0.478
5-min Apgar < 7	1 (4.2)	7 (10.9)	0.438
SES			0.593
- high	3 (12.5)	14 (22.2)	
- moderate	17 (70.8)	41 (65.1)	
- low	4 (16.7)	8 (12.7)	
Maternal education*			0.847
- high	3 (23.1)	8 (17.4)	
- moderate	6 (46.2)	20 (43.5)	
- low	4 (30.8)	18 (39.1)	
Multiple pregnancy	2 (8.3)	13 (20.3)	0.222
Maternal hypertension	19 (79.2)	36 (56.3)	0.082
NICU stay >28 days	23 (95.8)	54 (84.4)	0.276

	SGA no catch-up n=24	SGA catch-up n=64	No catch-up vs catch-up p-value
Ventilation			0.398
- no	4 (16.7)	15 (23.4)	
- <2 weeks	10 (41.7)	15 (23.4)	
- 2-4 weeks	7 (29.2)	21 (32.8)	
- >4 weeks	3 (12.5)	13 (20.3)	
Oxygen >21%	23 (95.8)	56 (87.5)	0.434
IRDS			**0.040**
-no	14 (58.3)	25 (39.1)	
-grade I/II	8 (33.3)	17 (26.6)	
-grade III/IV	2 (8.3)	22 (34.4)	
BPD	13 (54.2)	35 (54.7)	1.000
Hydrocortisone	11 (45.8)	32 (50.0)	0.813
Hypotension	16 (66.7)	40 (62.5)	0.807
PDA	8 (33.3)	17 (26.6)	0.599
PVL			0.126
- no	10 (41.7)	40 (62.5)	
- grade I	14 (58.3)	23 (35.9)	
- grade II	0	1 (1.6)	
IVH			0.087
- no	22 (91.7)	44 (68.8)	
- grade I/II	2 (8.3)	16 (25.0)	
- grade III/IV	0	4 (6.3)	
Septicaemia	15 (62.5)	39 (60.9)	1.000
NEC	1 (4.2)	7 (10.9)	0.438
Hyperbilirubinemia	19 (79.2)	52 (81.3)	1.000
Hypoglycaemia	6 (25.0)	16 (25.0)	1.000
Hyperglycaemia	3 (12.5)	22 (34.4)	0.062

SGA: small for gestational age: height (Ht) and/ or weight (Wt) at birth < -2sds. No catch-up growth: height (Ht) remained <-2sds, catch-up growth: Ht increased to ≥-2sds. GA: gestational age, BW: birth weight, OFC: occipital-frontal circumference, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 8b. Differing perinatal characteristics and neonatal morbidity between SGA children without catch-up growth and SGA with catch-up growth in weight/ height between birth and 5.5 years of age.

	SGA no catch-up n=18	SGA catch-up growth n=70	No catch-up vs catch-up p-value
Median GA (weeks) (min~max)	29.0 (25.7~34.4)	28.1 (24.8~33.8)	0.246
Median BW (gram) (min~max)	600 (480~740)	680 (480~750)	**<0.001**
Median birth length (cm) (min~max)	31.0 (17.0~35.0)	31.0 (21.0~34.5)	0.690
Median birth OFC (cm) (min~max)	23.3 (21.0~27.0)	23.2 (20.0~26.0)	0.639
Ethnicity	18 (100)	63 (90.0)	0.337
Male	5 (27.8)	34 (48.6)	0.183
5-min Apgar < 7	0	8 (11.4)	0.199
SES			0.252
- high	1 (5.9)	16 (22.9)	
- moderate	14 (82.4)	44 (62.9)	
- low	2 (11.8)	10 (14.3)	
Maternal education*			0.112
- high	3 (30.0)	8 (16.3)	
- moderate	6 (60.0)	20 (40.8)	
- low	1 (10.0)	21 (42.9)	
Multiple pregnancy	5 (27.8)	10 (14.3)	0.179
Maternal hypertension	10 (55.6)	45 (64.3)	0.588
NICU stay >28 days	15 (83.3)	62 (88.6)	0.689
Ventilation			0.703
- no	4 (22.2)	15 (21.4)	
- <2 weeks	7 (38.9)	18 (25.7)	
- 2-4 weeks	4 (22.2)	24 (34.3)	
- >4 weeks	3 (16.7)	13 (18.6)	
Oxygen >21%	16 (88.9)	63 (90.0)	1.000
IRDS			**0.047**
-no	7 (38.9)	32 (45.7)	
-grade I/II	9 (50.0)	16 (22.9)	
-grade III/IV	2 (11.1)	22 (31.4)	
BPD	9 (50.0)	39 (55.7)	0.792
Hydrocortisone	8 (44.4)	35 (50.0)	0.793
Hypotension	12 (66.7)	44 (62.9)	0.793
PDA	5 (27.8)	20 (28.6)	1.000

	SGA no catch-up n=18	SGA catch-up growth n=70	No catch-up vs catch-up p-value
PVL			0.677
- no	9 (50.0)	41 (58.6)	
- grade I	9 (50.0)	28 (40)	
- grade II	0	1 (1.4)	
IVH			0.792
- no	14 (77.8)	52 (74.3)	
- grade I/II	4 (22.2)	14 (20.0)	
- grade III/IV	0	4 (5.7)	
Septicaemia	10 (55.6)	44 (62.9)	0.596
NEC	0	8 (11.4)	0.199
Hyperbilirubinemia	15 (83.3)	56 (80.0)	1.000
Hypoglycaemia	3 (16.7)	19 (27.1)	0.543
Hyperglycaemia	2 (11.1)	23 (32.9)	0.083

SGA: small for gestational age: height (Ht) and/ or weight (Wt) at birth < -2sds. No catch-up growth: weight/ height (Wt/ Ht) remained <-2sds, catch-up growth: Wt/Ht increased to ≥-2sds, GA; gestational age, BW: birth weight, OFC: occipital-frontal circumference, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 8c. Differing perinatal characteristics and neonatal morbidity between SGA children without catch-up growth and SGA with catch-up growth in weight between birth and 5.5 years of age.

	SGA no catch-up n=38	SGA catch-up n=50	No catch-up vs catch-up p-value
Median GA (weeks) (min~max)	29.0 (25.7~34.4)	27.8 (24.8~33.8)	**0.002**
Median BW (gram) (min~max)	629 (480~750)	697 (530~750)	**0.002**
Median birth length (cm) (min~max)	31.0 (21.0~35.0)	31.0 (28.0~35.0)	0.535
Median birth OFC (cm) (min~max)	23.0 (21.0~27.0)	23.5 (20.0~26.0)	0.264
Ethnicity (Caucasian)	36 (94.7)	45 (90.0)	0.694
Male	16 (42.1)	23 (46.0)	0.829
5-min Apgar < 7	1 (2.6)	7 (14.0)	0.131
SES			0.725
- high	8 (21.6)	9 (18.0)	
- moderate	23 (62.2)	35 (70.0)	
- low	6 (16.2)	6 (12.0)	

	SGA no catch-up n=38	SGA catch-up n=50	No catch-up vs catch-up p-value
Maternal education*			0.420
- high	4 (16.7)	7 (20.0)	
- moderate	13 (54.2)	13 (37.1)	
- low	7 (29.2)	15 (42.9)	
Multiple pregnancy	7 (18.4)	8 (16.0)	0.782
Maternal hypertension	24 (63.2)	31 (62.0)	1.000
NICU stay >28 days	32 (84.2)	45 (90.0)	0.520
Ventilation			0.784
- no	10 (26.3)	9 (18.0)	
- <2 weeks	11 (28.9)	14 (28.0)	
- 2-4 weeks	11 (28.9)	17 (34.0)	
- >4 weeks	6 (15.8)	10 (20.0)	
Oxygen >21%	33 (86.8)	46 (92.0)	0.492
IRDS			**0.023**
-no	22 (57.9)	17 (34.0)	
-grade I/II	11 (28.9)	14 (28.0)	
-grade III/IV	5 (13.2)	19 (38.0)	
BPD	21 (55.3)	27 (54.0)	1.000
Hydrocortisone	17 (44.7)	26 (52.0)	0.526
Hypotension	23 (60.5)	33 (66.0)	0.658
PDA	13 (34.2)	12 (24.0)	0.344
PVL			**0.004**
- no	15 (39.5)	35 (70.0)	
- grade I	23 (60.5)	14 (28.0)	
- grade II	0	1 (2.0)	
IVH			0.099
- no	33 (86.8)	33 (66.0)	
- grade I/II	4 (10.5)	14 (28.0)	
- grade III/IV	1 (2.6)	3 (6.0)	
Septicaemia	23 (60.5)	31 (62.0)	1.000
NEC	2 (5.3)	6 (12.0)	0.457
Hyperbilirubinemia	32 (84.2)	39 (78.0)	0.589
Hypoglycaemia	10 (26.3)	12 (24.0)	0.809
Hyperglycaemia	9 (23.7)	16 (32.0)	0.477

SGA: small for gestational age: height (Ht) and/ or weight (Wt) at birth < -2sds. No catch-up: weight (Wt) remained <-2sds, catch-up growth: Wt increased to ≥-2sds, GA; gestational age, BW: birth weight, OFC: occipital-frontal circumference, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 8d. Differing perinatal characteristics and neonatal morbidity between SGA children without catch-up growth and SGA with catch-up growth in OFC between birth and 5.5 years of age.

	SGA no catch-up n=38	SGA catch-up growth n=30	No catch-up vs catch-up p-value
Median GA (weeks) (min~max)	29.0 (26.3~34.4)	28.1 (24.8~31.1)	**0.031**
Median BW (gram) (min~max)	637 (480~750)	655 (480~750)	0.591
Median birth length (weeks) (min~max)	31.0 (27.0~34.0)	30.5 (21.0~35.5)	0.739
Median birth OFC (cm) (min~max)	23.0 (21.0~25.5)	23.0 (20.0~26.0)	0.875
Ethnicity (Caucasian)	34 (89.5)	28 (93.3)	0.687
Male	16 (42.1)	13 (43.3)	1.000
5-min Apgar < 7	1 (2.6)	5 (16.7)	0.080
SES			0.585
- high	6 (15.8)	7 (23.3)	
- moderate	27 (71.1)	21 (70.0)	
- low	5 (13.2)	2 (6.7)	
Maternal education*			0.830
- high	3 (14.3)	2 (9.1)	
- moderate	12 (57.1)	12 (54.5)	
- low	6 (28.6)	8 (36.4)	
Multiple pregnancy	5 (13.2)	5 (16.7)	0.740
Maternal hypertension	24 (63.2)	18 (60.0)	0.807
NICU stay >28 days	32 (84.2)	26 (86.7)	1.000
Ventilation			0.738
- no	10 (26.3)	7 (23.3)	
- <2 weeks	10 (26.3)	9 (30.0)	
- 2-4 weeks	11 (28.9)	11 (36.7)	
- >4 weeks	7 (18.4)	3 (10.0)	
Oxygen >21%	35 (92.1)	26 (86.7)	0.691
IRDS			0.380
-no	21 (55.3)	14 (46.7)	
-grade I/II	11 (28.9)	7 (23.3)	
-grade III/IV	6 (15.8)	9 (30.0)	
BPD	18 (47.4)	16 (53.3)	0.807
Hydrocortisone	15 (39.5)	13 (43.3)	0.807
Hypotension	22 (57.9)	19 (63.3)	0.803
PDA	13 (34.2)	5 (16.7)	0.166

	SGA no catch-up n=38	SGA catch-up growth n=30	No catch-up vs catch-up p-value
PVL			0.616
- no	18 (47.4)	15 (50.0)	
- grade I	20 (52.6)	14 (46.7)	
- grade II	0	1 (3.3)	
IVH			0.800
- no	30 (78.9)	23 (76.7)	
- grade I/II	7 (18.4)	5 (16.7)	
- grade III/IV	1 (2.6)	2 (6.7)	
Septicaemia	27 (71.1)	18 (60.0)	0.440
NEC	4 (10.5)	3 (10.0)	1.000
Hyperbilirubinemia	28 (73.7)	26 (86.7)	0.236
Hypoglycaemia	7 (18.4)	11 (36.7)	0.105
Hyperglycaemia	5 (13.2)	11 (36.7)	**0.042**

SGA: small for gestational age: occipital-frontal circumference (OFC) at birth <p10. No catch-up growth: OFC remained <p10, catch-up growth: OFC increased to ≥p10, GA: gestational age, BW: birth weight, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 9a. Differing perinatal characteristics and neonatal morbidity between AGA children with adequate growth and AGA with catch-down growth in height between birth and 5.5 years of age.

	AGA adequate n=11	AGA catch-down n=2	Adequate vs catch-down p-value
Median GA (weeks) (min~max)	26.0 (25.0~27.4)	27.8 (27.7~27.8)	**0.013**
Median BW (gram) (min~max)	739 (660~750)	670 (650~690)	0.128
Median birth length (cm) (min~max)	33.0 (32.5~37.0)	35.7 (35.5~35.8)	0.167
Median birth OFC (cm) (min~max)	22.8 (22.0~29.0)	27.8 (26.5~29.0)	0.106
Ethnicity (Caucasian)	10 (90.9)	2 (100)	1.000
Male	6 (54.5)	0	0.462
5-min Apgar < 7	4 (36.4)	0	1.000
SES			0.462
- high	4 (36.4)	0	
- moderate	4 (36.4)	2 (100)	
- low	3 (27.3)	0	

	AGA adequate n=11	AGA catch-down n=2	Adequate vs catch-down p-value
Maternal education*			1.000
- high	1 (16.7)	0	
- moderate	1 (16.7)	1 (50.0)	
- low	4 (66.7)	1 (50.0)	
Multiple pregnancy	5 (45.5)	0	0.487
Maternal hypertension	2 (18.2)	2 (100)	0.077
NICU stay >28 days	9 (81.8)	1 (50.0)	0.423
Ventilation			0.590
- no	1 (9.1)	0	
- <2 weeks	4 (36.4)	0	
- 2-4 weeks	6 (54.5)	2 (100)	
- >4 weeks	0	0	
Oxygen >21%	11 (100)	2 (100)	1.000
IRDS			0.462
-no	4 (36.4)	0	
-grade I/II	3 (27.3)	0	
-grade III/IV	4 (36.4)	2 (100)	
BPD	7 (63.6)	2 (100)	1.000
Hydrocortisone	5 (45.5)	2 (100)	0.462
Hypotension	5 (45.5)	2 (100)	0.462
PDA	8 (72.7)	1 (50.0)	1.000
PVL			0.462
- no	6 (54.5)	0	
- grade I	5 (45.5)	2 (100)	
- grade II	0	0	
IVH			1.000
- no	7 (63.6)	2 (100)	
- grade I/II	4 (36.4)	0	
- grade III/IV	0	0	
Septicaemia	7 (63.6)	1 (50.0)	1.000
NEC	1 (9.1)	0	1.000
Hyperbilirubinemia	8 (72.7)	1 (50.0)	1.000
Hypoglycaemia	2 (18.2)	0	1.000
Hyperglycaemia	3 (27.3)	1 (50.0)	1.000

AGA: appropriate for gestational age: height (Ht) and/ or weight (Wt) at birth ≥ -2sds. Adequate growth: Ht remained ≥ -2sds, catch-down growth: Ht decreased to <-2sds, GA; gestational age, BW: birth weight, OFC: occipital-frontal circumference, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 9b. Differing perinatal characteristics and neonatal morbidity between AGA children with adequate growth and AGA with catch-down growth in weight/ height between birth and age 5.5.

	AGA adequate n=13	AGA catch-down n=0	Adequate vs catch-down p-value
Median GA (weeks) (min~max)	26.1 (25.0~27.8)		-
Median BW (gram) (min~max)	735 (650~750)		-
Median birth length (cm) (min~max)	33.0 (32.5~37.0)		-
Median birth OFC (cm) (min~max)	23.3 (22.0~29.0)		-
Ethnicity	12 (93.3)		-
Male	6 (46.2)		-
5-min Apgar < 7	4 (30.8)		-
SES			-
- high	4 (30.8)		
- moderate	6 (46.2)		
- low	3 (23.1)		
Maternal education*			-
- high	1 (12.5)		
- moderate	2 (25.0)		
- low	5 (62.5)		
Multiple pregnancy	5 (38.5)		-
Maternal hypertension	4 (30.8)		-
NICU stay >28 days	10 (76.9)		-
Ventilation			-
- no	1 (7.7)		
- <2 weeks	4 (30.8)		
- 2-4 weeks	8 (61.5)		
- >4 weeks	0		
Oxygen >21%	13 (100)		-
IRDS			-
-no	4 (30.8)		
-grade I/II	3 (23.1)		
-grade III/IV	6 (46.2)		
BPD	9 (69.2)		-
Hydrocortisone	7 (53.8)		-
Hypotension	7 (53.8)		-
PDA	9 (69.2)		-
PVL			-
- no	6 (46.2)		
- grade I	7 (53.8)		
- grade II	0		

	AGA adequate n=13	AGA catch-down n=0	Adequate vs catch-down p-value
IVH			-
- no	9 (69.2)		
- grade I/II	4 (30.8)		
- grade III/IV	0		
Septicaemia	8 (61.5)		-
NEC	1 (7.7)		-
Hyperbilirubinemia	9 (69.2)		-
Hypoglycaemia	2 (15.4)		-
Hyperglycaemia	4 (30.8)		-

Appropriate for gestational age: AGA: height (Ht) and/ or weight (Wt) at birth ≥ -2sds. Adequate growth: weight/ height (Wt/Ht) remained ≥-2sds, catch-down growth: Wt/Ht decreased to <-2sds, GA: gestational age, BW: birth weight, OFC: occipital-frontal circumference, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 9c. Differing perinatal characteristics and neonatal morbidity between AGA children with adequate growth and AGA with catch-down in weight between birth and 5.5 years of age.

	AGA adequate n=9	AGA catch-down n=4	Adequate vs catch-down p-value
Median GA (weeks) (min~max)	26.0 (25.0~27.4)	27.0 (25.3~27.8)	0.214
Median BW (gram) (min~max)	739 (660~750)	690 (650~750)	0.439
Median birth length (cm) (min~max)	33.0 (32.5~37.0)	34.8 (33.0~35.8)	0.224
Median birth OFC (cm) (min~max)	22.8 (22.5~29.0)	25.0 (22.0~29.0)	0.582
Ethnicity (Caucasian)	8 (88.9)	4 (100)	1.000
Male	6 (66.7)	0	0.070
5-min Apgar < 7	4 (44.4)	0	0.228
SES			0.259
- high	4 (44.4)	0	
- moderate	3 (33.3)	3 (75.0)	
- low	2 (22.2)	1 (25.0)	
Maternal education*			1.000
- high	1 (20.0)	0	
- moderate	1 (20.0)	1 (33.3)	
- low	3 (60.0)	2 (66.7)	

	AGA adequate n=9	AGA catch-down n=4	Adequate vs catch-down p-value
Multiple pregnancy	3 (33.3)	2 (50.0)	1.000
Maternal hypertension	2 (22.2)	2 (50.0)	0.530
NICU stay >28 days	7 (77.8)	3 (75.0)	1.000
Ventilation			1.000
- no	1 (11.1)	0	
- <2 weeks	3 (33.3)	1 (25.0)	
- 2-4 weeks	5 (55.6)	3 (75.0)	
- >4 weeks	0	0	
Oxygen >21%	9 (100)	4 (100)	-
IRDS			0.471
-no	3 (33.3)	1 (25.0)	
-grade I/II	3 (33.3	0	
-grade III/IV	3 (33.3)	3 (75.0)	
BPD	5 (55.6)	4 (100)	0.228
Hydrocortisone	4 (44.4)	3 (75.0)	0.559
Hypotension	4 (44.4)	3 (75.0)	0.559
PDA	6 (66.7	3 (75.0)	1.000
PVL			0.070
- no	6 (66.7)	0	
- grade I	3 (33.3)	4 (100)	
- grade II	0	0	
IVH			0.228
- no	5 (55.6)	4 (100)	
- grade I/II	4 (44.4)	0	
- grade III/IV	0	0	
Septicaemia	6 (66.7)	2 (50.0)	1.000
NEC	0	1 (25.0)	0.308
Hyperbilirubinemia	7 (77.8)	2 (50.0)	0.530
Hypoglycaemia	2 (22.2)	0	1.000
Hyperglycaemia	2 (22.2)	2 (50.0)	0.530

Appropriate for gestational age: AGA: height (Ht) and/ or weight (Wt) at birth ≥ -2sds. Adequate growth: Wt remained ≥-2sds, catch-down growth: Wt decreased to <-2sds, GA: gestational age, BW: birth weight, OFC: occipital-frontal circumference, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

Table 9d. Differing perinatal characteristics and neonatal morbidity between AGA children with adequate growth and AGA with catch-down growth in OFC between birth and 5.5 years of age.

	AGA adequate n=27	AGA catch-down n=6	Adequate vs catch-down p-value
Median GA (weeks) (min~max)	26.3 (25.0~28.4)	26.9 (25.7~31.0)	0.377
Median BW (gram) (min~max)	725 (600~750)	650 (580~750)	0.065
Median birth length (cm) (min~max)	32.5 (30.0~37.0)	33.0 (29.0~35.8)	0.625
Median birth OFC (cm) (min~max)	24.0 (22.0~29.0)	23.5 (23.0~29.0)	0.792
Ethnicity (Caucasian)	25 (92.6)	6 (100)	1.000
Male	15 (55.6)	1 (16.7)	0.175
5-min Apgar < 7	6 (22.2)	0	0.563
SES			1.000
- high	7 (25.9)	1 (20.0)	
- moderate	13 (48.1)	3 (60.0)	
- low	7 (25.9)	1 (20.0)	
Maternal education*			0.794
- high	6 (30.0)	1 (25.0)	
- moderate	4 (20.0)	0	
- low	10 (50.0)	3 (75.0)	
Multiple pregnancy	8 (29.6)	2 (33.3)	1.000
Maternal hypertension	13 (48.1)	4 (66.7)	0.656
NICU stay >28 days	24 (88.9)	5 (83.3)	1.000
Ventilation			0.845
- no	2 (7.4)	1 (16.7)	
- <2 weeks	9 (33.3)	1 (16.7)	
- 2-4 weeks	11 (40.7)	3 (50.0)	
- >4 weeks	5 (18.5)	1 (16.7)	
Oxygen >21%	26 (96.3)	5 (83.3)	0.335
IRDS			1.000
-no	7 (25.9)	1 (16.7)	
-grade I/II	8 (29.6)	2 (33.3)	
-grade III/IV	12 (44.4)	3 (50.0)	
BPD	18 (66.7)	5 (83.3)	0.640
Hydrocortisone	17 (63.0)	5 (83.3)	0.637
Hypotension	17 (63.0)	5 (83.3)	0.637
PDA	13 (48.1)	3 (50.0)	1.000

	AGA adequate n=27	AGA catch-down n=6	Adequate vs catch-down p-value
PVL			0.053
- no	21 (77.8)	2 (33.3)	
- grade I	6 (22.2)	4 (66.7)	
- grade II	0	0	
IVH			0.298
- no	16 (59.3)	6 (100)	
- grade I/II	10 (37.0)	0	
- grade III/IV	1 (3.7)	0	
Septicaemia	15 (55.6)	2 (33.3)	0.398
NEC	1 (3.7)	1 (16.7)	0.335
Hyperbilirubinemia	22 (81.5)	4 (66.7)	0.584
Hypoglycaemia	6 (22.2)	0	0.563
Hyperglycaemia	11 (40.7)	2 (33.3)	1.000

AGA: appropriate for gestational age: occipital-frontal circumference (OFC) at birth ≥p10. Adequate growth: OFC remained ≥p10, catch-down growth: OFC decreased to <p10, GA: gestational age, BW: birth weight, SES: socio-economic status, *maternal educational level was available for n=67, NICU: neonatal intensive care unit, IRDS: infant respiratory distress syndrome, BPD: bronchopulmonary dysplasia, PVL: periventricular leukomalacia, IVH: intraventricular haemorrhage, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus.

List of abbreviations

AGA	appropriate for gestational age
BMI	body mass index.
BSID-II	Bayley Scales of Infant Development- second edition
BPD	bronchopulmonary dysplasia
BW	birth weight
CA	corrected age
CBCL	Child Behaviour Checklist
CI	confidence interval
CP	cerebral palsy
DQ	developmental quotient
DVT	deep venous thrombosis
EH	eye-hand coordination
ELBW	extremely low birth weight
GA	gestational age
g	gram
GH	growth hormone
GMDS	Griffiths Mental Developmental Scales
HFOV	high frequency oscillatory ventilation
Ht	height
IRDS	infant respiratory distress syndrome
IQ	intelligence quotient
IUGR	intra-uterine growth restriction
IVH	intraventricular haemorrhage
LM	locomotor
M-ABC	Movement Assessment Battery for Children
Max	maximum
MDI	Mental Development Index
Min	minimum
NDO	neurodevelopmental outcome
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NPV	negative predictive value
OFC	occipital-frontal circumference
PDA	patent ductus arteriosus
PDI	Psychomotor Development Index
PE	pulmonary embolism
PPROM	preterm premature rupture of membrane
PPV	positive predictive value
PRN	perinatal registry of the Netherlands

PVL	periventricular leukomalacia
RAKIT	Revisie Amsterdamse Kinder Intelligentie Test
ROP	retinopathy of prematurity
SD	standard deviation
SDS	standard deviation score
SDSHtcorr	SDS height corrected for TH
SES	socio- economic status
SGA	small for gestational age
SON-R	Snijders-Oomen Nonverbal Revised intelligence test
TIS	Total Impairment Score
TH	target height
TTS	total test score
TRF	Teacher Report Form
UCA	uncorrected age
Vs	versus
VLBW	very low birth weight
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
Wt	weight
Wt/Ht	weight for height

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List of publications

Claas MJ, Bruinse HW, van der Heide-Jalving M, Termote JUM, de Vries LS. Changes in survival and neonatal morbidity in infants with a birth weight of 750 g or less. Neonatology 2010;98:278-288.

Claas MJ, Bruinse HW, Koopman C, van Haastert IC, Peelen LM, de Vries LS. 2-year neurodevelopmental outcome of preterm born children ≤ 750 gram at birth. Arch Dis Child Fetal Neonatal Ed 2010 Jun 7 [Epub ahead of print].

Claas MJ, Timmermans A, Bruinse HW. Case report: a black and white twin. J Perinatol 2010 June;30, 434-436.

Claas MJ, van Haastert IC, Bruinse HW, Uniken Venema MMA, de Vries LS, Koopman C. Het testen van de cognitieve en motorische ontwikkeling van kinderen. Wat meten we, wanneer en met welke test? Submitted.

Claas MJ, de Vries LS, Bruinse HW, van Haastert IC, Uniken Venema MMA, Peelen LM, Koopman C. Neurodevelopmental outcome over time of preterm born children ≤ 750 gram at birth. Submitted.

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Lieve Guido, nog niet zo lang maar wel heel fijn. Stress, altijd de laptop aan, die tijd is nu echt voorbij. Dankjewel voor je begrip de afgelopen tijd. Heb heel veel zin in onze vakantie (zonder laptop!).

Lieve zusjes Anne, Floor en Carlijn, dankjewel voor alle steun, interesse en gezelligheid de afgelopen jaren. Floor, nogmaals sorry van je laptop…
Ik ben echt superblij met zulke zusjes en dat jullie als paranimfen naast mij staan!!

Curriculum vitae

Marieke Claas werd op 28 oktober 1981 te Leiderdorp geboren als tweede van vier zusjes. Zij behaalde in 2000 haar Gymnasium diploma aan het Bonaventura college te Leiden. In de zomerperiode na haar eindexamen is Marieke naar Kenia gereisd om vrijwilligerswerk te doen in een weeshuis, waar haar interesse in ontwikkelingshulp is aangewakkerd.

In 2001 begon zij met de studie Geneeskunde aan de Universiteit Utrecht. Tijdens haar studie heeft zij in 2004 het co-schap gynaecologie in het St. Francis Hospital te Zambia gedaan en aansluitend een keuze onderzoek naar sectio gerelateerde complicaties in het Bottom Hospital in Malawi. Naast de co-schappen in Nederland, vertrok zij in 2006 voor twee maanden naar Maleisië voor een co-schap spoedeisende hulp in Hospital Kuala Lumpur. In het laatste jaar van haar studie (2007) deed zij de keuze co-schappen neonatologie (Wilhelmina Kinderziekenhuis te Utrecht) en urologie (Diakonessenhuis te Utrecht), gevolgd door een semi-arts stage gynaecologie en verloskunde (Tergooiziekenhuizen te Hilversum), en een wetenschappelijke stage onder supervisie van prof. dr. H.W. Bruinse en prof. dr. L.S. de Vries, welke de basis vormt voor dit promotie onderzoek. In augustus 2007 behaalde Marieke cum laude haar artsdiploma aan de Universiteit Utrecht.

Na haar afstuderen werkte zij gedurende anderhalf jaar als arts-assistent gynaecologie in het Meander Medisch Centrum in Amersfoort. In samenwerking met dr. M.J. Duk zette zij een onderzoek naar vitamine D deficiëntie en vermoeidheid bij gynaecologisch oncologische patiënten op. In 2009 startte zij als arts-assistent op de afdeling verloskunde in het Wilhelmina Kinderziekenhuis te Utrecht. Tijdens haar werkzaamheden als arts-assistent heeft zij haar promotie onderzoek uitgevoerd onder begeleiding van prof. dr. L.S. de Vries, prof. dr. H.W. Bruinse en dr. C. Koopman. Op het Gynaecongres in Breda ontving zij onlangs de Willem Schellekens prijs voor haar presentatie ‘Neonaten met een geboortegewicht ≤ 750g: cognitieve ontwikkeling op 2-jarige leeftijd’.

In mei 2010 startte zij met de opleiding tot gynaecoloog in het Sint Elisabeth Ziekenhuis te Tilburg (opleider dr. H.A.M. Vervest).